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CONTRIBUTIONS  
TO THE SCIENCE OF  
M E D I C I N E  
AND OF PHYSIOLOGY.

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SECOND SERIES.

Being a collection of the Journal Publications  
of this Author

From 1902 to 1914,

BY

THOMAS L. PATTERSON, M. A.,

Associate Professor of Physiology in the University of Maryland.

AND

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Associate in Physiology.

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Baltimore, Md., November, 1914.

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**INTESTINAL INDIGESTION  
(DYSTRYPSIA).**

BY  
**JOHN C. HEMMETER, PH.D., M.D., Etc.,**  
OF BALTIMORE, MD.

FROM  
**THE MEDICAL NEWS,**  
NEW YORK,  
APRIL 18, 1903.



[Reprinted from THE MEDICAL NEWS, April 18, 1903.]

### INTESTINAL INDIGESTION (DYSTRYPSIA).\*

BY JOHN C. HEMMETER, PH.D., M.D., ETC.,  
OF BALTIMORE, MD.;

PROFESSOR IN THE MEDICAL DEPARTMENT, UNIVERSITY OF MARY-  
LAND; DIRECTOR OF THE CLINICAL LABORATORY, ETC.

AS I UNDERSTOOD your President, I was to give not an exhaustive report, but a critical and instructive summing up of that which is of clinical significance and of practical importance concerning Dystrypsia, and to present this as conceived through personal critical experience.

We are living in a period in the history of medicine in which the experimental tendency has gained supremacy over speculative philosophy in medicine. But we are in the possession of such an enormous amount of new material and facts, which by additional experiments is daily increasing, that the new facts frequently must be allowed to remain unused and are, for the time being, of no assistance in the advancement of our science. In this connection I must again repeat what I have emphasized in the preface of the second volume of my work on "Diseases of the Intestines," namely, the difference between *truth* and mere *facts*. These two are often, unfortunately, considered synonymous. Facts are little truths that our senses are capable, for the present, of comprehending, but back of and beyond these facts later experience often reveals the higher and greater truth. An experimental fact which to-day seems absolutely disconnected and therefore without meaning, may to-morrow, when viewed in

\* Address before the New York Academy of Medicine, Section on General Medicine, December 16, 1902.

another light, suddenly assume a far-reaching significance and importance. No new fact of experience, be it at present apparently ever so remote from practical understanding, need be considered worthless—provided it is correct. It may be allowed to rest as raw material for a time, but it is probable that in another association, it may acquire an importance which we did not anticipate.

But this I must emphasize, that an isolated, disconnected fact of experience or experiment, has for the time being no significance for the progress of medicine. This significance comes only then when we can arrange and fix this fact into the already existing and firmly established architecture of our knowledge. There exists a danger in overrating the value of single facts of experience and experiment. Individual facts discovered this way are accumulating to such an extent that we are completely submerged under an ocean of experimental results, and the intellectual interpretation which fits them into the synthetic structure of our science is missing. Physicians who are not participants in experimental undertaking, feel this absence of the connecting links between an enormous number of new acquisitions very painfully, which, though experimental, are in a sense empirical. This is also true of the experimental acquisitions in bacteriological as well as biochemical domains. In the eighteenth and during the first part of the nineteenth centuries medicine was comparable to a sterile unproductive heath, in which some evil spirit drove about the speculative medical philosophers in a circle. Now we have gotten into an overfruitful swamp or jungle in which the facts grow so luxuriantly that they threaten to smother our thinking powers. The tendency of all new laboratories is to bring out new facts. Let us



have all of them if it must be, but what we need as much, if not more than new facts, are master minds who will instruct us in the interpretation of these facts, and give them a meaning and value by fitting them into the synthetic structure of medicine. Martius (*Pathogenese innerer Krankheiten*) compares modern medicine to a sense-confusing concert, and what is needed is a disciplinarian to instruct us concerning the leading "*motives*," to seek the familiar law in the revealed wonders of the present time.

"Sucht das vertraute Gesetz in des Zufalls grausenden Wundern,

Sucht den ruhenden Pol in der Erscheinungen Flucht."

—Schiller.

Alexander von Humboldt, in his monumental work "*Kosmos*," describes the condition of the mind in one to whom a promised land of research of any kind has opened itself, in a very beautiful manner. The following are his words: "It is a custom of those who would like to conduct others to the summit of mountains, to describe the path as pleasanter and easier as it will be found in reality. It is their habit to praise the glorious views from the mountains, even though they may divine that large portions of the regions below may be concealed in fog. They know also that in this concealment there is a mysterious charm and that in a hazy perspective distance the impression of infinity will be made reflecting in a serious and divining manner in the mind and in the sentiments." And I may add that this feeling of mysterious charm will in the right kind of a mind elicit the desire of a closer acquaintance with that region seemingly so far away; and this is about the conception that I have of the sentiments with which an investigator should approach the solution of difficult problems of any

kind. The stimulation which comes from everything that is new and understood makes us put up with many a stony path and much hard work, in seeking further knowledge. In connection with the accumulation of single facts of experience and experiment in medicine, the correlation of which with our general knowledge of already established truths has not yet taken place, Humboldt says: "It is a safe criterion of the quantity and quality of the discoveries which we may expect in any science, when the facts seem yet to stand isolated and without relation to another." The great plethora of experimental results, therefore, is rather to be interpreted as a good sign, only we will have to be cautious not to regard in the light of a law what is in reality only a recent acquisition standing, as a rule, in very loose relation or having no connection at all with the synthetic structure of medical knowledge.

Our main efforts in diagnosis will as a rule be directed to separate the intestinal neuroses from bowel diseases with a distinct anatomical substratum. The most frequent of the latter are the various types of enteritis. In acute enteritis of the jejunum and ileum most important objective evidences are found in abnormal condition of stools, mostly diarrheic and thick like gruel—characteristic features are (1) shreds of *mucus* intimately admixed with the fecal matter, (2) *bile pigments*, (3) *epithelia and muscle fibers* stained with bile. If stool is solid a *test lavage of colon* should be made to differentiate catarrh of small from that of large intestine; if the lavage water brings out large connected shreds of mucus or membranes or masses of glassy mucus, we have a colitis. We may have an enteritis at the same time, but this cannot be definitely established if the colitis is certainly

present. Enteritis running its course with obstipation has no characteristic subjective symptoms. The objective signs are bile pigments, the constant presence of abundant muscle fibers and well-recognizable starch cells, and of fat in form of oil droplets, fatty acid crystals or soaps. The exact localization of catarrh of the small intestine is practically impossible.

*Dyspeptic Diarrhea in Connection with Stomach Diseases.*—In the gastric condition known as achylia gastrica—complete loss or suppression of gastric secretion (HCl and ferments)—we may encounter severe diarrheas, during which the subjective gastric symptoms are completely submerged under the clinical picture of what looks like acute enteritis. This occurs also in the abnormality of gastric secretion which I have first called attention to and designated as "*Heterochylia*" (from ἑτερος, meaning "other," or different, varying, and χυλός, meaning juice). (See Hemmeter, "Diseases of the Stomach," third edition, p. 870.) For the recognition of this dyspeptic diarrhea test-meal analysis is indispensable, and stool examination necessary. The gastric peristalsis is unimpaired as a rule, but chymification absent entirely. The feces show unchanged residue of meat, connective tissue, especially vegetable foods and even fat residues. The work of Pawlow has shown conclusively that the gastric HCl is the most essential stimulation to the formation of pancreatic juice. In his masterly research Pawlow discovered a new enzyme in gastric secretion—a specific ferment—chymaze, which does not digest food, but which accelerates the action of the ferments of the pancreatic secretion. The digestive tract is not universally and uniformly irritable or stimulatable by every mechanical, chemical, thermic or dietetic agent, but there is a specific irritability and a specific reaction

with regard to the peculiarity of every individual digestive demand or duty. There is a most artistic digestive mechanism of digestion revealed by Pawlow's work, which in its sublime fineness, preciseness and accuracy and inner adaptiveness to utility and purpose exceeds any new discovery of modern physiology. If you want to feel proud of being a physician, if you wish to feel the ennobling consciousness and enthusiasm that comes from successful, hard and earnest work, from difficulties overcome, read Pawlow's "Die Arbeit der Verdauungsdrüsen."

The most efficient means of counteracting dyspepsia due to pancreatic insufficiency is to bring about a healthy appetite. Appetite is the stimulus to normal gastric secretion, and this in turn the normal stimulant to healthy pancreatic secretion.

Although an article on intestinal dyspepsia is not the proper place to consider the newer gastric physiology, a brief reference to recent discoveries is indispensable—not simply because the stomach is the preparatory organ for intestinal digestion, but also because the chemical processes which various food-articles undergo in the stomach are of far-reaching importance for the changes which are to occur in these foods after they reach the intestines. Many of the older authors, beginning with the American physiologist Beaumont, believe that the mechanical irritation of the foods cause the gastric secretion, but the experiments in Pawlow's laboratory have proved the fallacy of this view. In the first place, if the secretion were due to simple mechanical irritation, there is no reason why irritation with the point of a glass rod, with a feather, or with sand placed in the stomach, should not cause the secretion also. The mistake of the older experimenters, according to Pawlow, grew out of the fact that they ignored the so-called psychic secre-

tion—a secretion which can be set up by the mere smell of food, or even by a very intense feeling of hunger. If the esophagus of a dog is cut, and its end sewed to the edges of an abdominal wound, and at the same time a gastric fistula is established, pieces of meat which are fed to the dog after healing of these fistulæ, will not reach the stomach, but fall out of the upper end of the fistula leading into the esophagus. Nevertheless in five or six minutes after swallowing the food gastric juice begins to be secreted, running from the gastric canula first in drops and afterward in a continuous stream. If the dog be offered meat without receiving it, the gastric secretion will also appear, though not so plentifully as when the dog was actually allowed to eat the meat. A further interesting phenomenon observed on these dogs was that no secretion followed the swallowing indigestible substances like small stones. These experiments furthermore elicited the astounding fact that for every kind of food a definite gastric secretion is formed of specific composition. Therefore we can say that the stomach provides a certain chemical agent to meet each case. We must therefore conclude that the mucous membrane of the stomach is capable of distinguishing between the varieties and classes of food that come in contact with it, much as the skin recognizes mechanical, chemical, thermic and electrical stimulation. The question might be asked "What is the object of this psychic secretion?" for Pawlow has clearly established the existence of two kinds of gastric secretion, the chemic and the psychic. This question applied to the human physiology would be the same as inquiring "What is the object of appetite?" The answer is that under the influence of the psychic secretion a gastric juice is furnished which is much more effective than that which is secreted



under purely chemical stimulation of the food, *i.e.*, when food is taken without any special appetite. Furthermore, under the influence of psychic secretion foods which otherwise would not stimulate the gastric mucosa to secretion become converted by the already present psychic secretion into something else which constitutes a further stimulant to the secretion of gastric juice. For instance, if a solution of albumin be administered to a dog upon which a Pawlow operation has been performed, (*i.e.*, splitting off part of the stomach, with all the vessels and nerves intact, and making this second smaller stomach communicate with the external abdominal wall, but not with the general cavity of the large stomach from which it is dissected (See International Clinics, XII series, Vol. II, p. 276)—there will be no secretion from the small stomach, for albumin by itself does not excite chemical secretion. But if the psychic secretion is set up by some other means, before the albumin is placed in the large stomach—for instance, by waving a piece of meat before the dog's eyes—then following the introduction of albumin, a secretion will be found in the small stomach which is qualitatively and quantitatively greater than the psychic secretion alone, or when albumin is given alone it is evident that while albumin in itself does not excite secretion, the products of albumin do cause this secretion. The same is true of pieces of bread which when placed in the large stomach through the fistula will not promote a secretion, but if the dog is allowed to swallow the bread, secretion commences and continues for several hours. Psychic secretion, therefore, is a preparatory secretion, transforming substances which would otherwise not stimulate the stomach, into such conditions which can accomplish this stimulation. The fact that bread will cause a secretion

when chewed and swallowed and not when placed directly in the stomach through the fistula, may be interpreted (as Pawlow and Peter Borisoff do), as proving the secretion of a gastric juice under psychic influence but—as I will show presently—it may be due to a special ferment in the saliva that stimulates gastric secretion.

Further revelations from Pawlow's laboratory disclose very important relations between the various classes of food, permitting the conclusion that they may mutually advance or interfere with the digestion of their various constituents in the gastric chyme. For instance, starch paste does not by itself promote gastric secretion, but when mixed with meat it was found to accelerate the action of the gastric juice, increasing its digestive power. On the other hand the addition of fat to a meat diet diminished the quantity of gastric secretion as well as its digestive power. Furthermore, it was demonstrated that the stomach is capable of distinguishing between lactic, butyric and hydrochloric acids, and responded to each of these acids with a varying quantitative secretion. As lactic and butyric acids are products of gastric fermentation, their stimulating influence on gastric secretion is of therapeutic importance. It is evident therefore that the stomach is extremely delicate in detecting not only the composition of foods and regulating the composition of its secretion correspondingly, but that it can distinguish between various organic acids. These experiments furthermore gave the clue to the treatment of gastric secretory disorders not by drugs merely, but by dietetic measures.

I have dwelt upon these results because disordered gastric digestion is, in my opinion, very often the cause of intestinal dyspepsia. By these gastric disorders I do not necessarily mean the organic diseases of the stomach (gastritis, ulcers,

etc.), but simply the improper composition of the diet causing abnormal chemical formations in the chyme; and as a healthy gastric digestion is a necessary precursor to a normal pancreatic secretion and duodenal digestion, a reference to these results requires no apology. Referring once more to the new gastric ferment "chymaze," which does not digest food but accelerates the action of the pancreatic ferments, it may interest you to learn that I have discovered in normal saliva a ferment which, if added to digesting mixtures of gastric juice, accelerates the digestive power of the gastric secretion. In other words, this new salivary ferment will effect a more rapid conversion of proteid into the albumoses and peptones, a quicker solution of boiled egg albumin and of fibrin, than would occur without it. I have proposed the name "*salivary secretion*" for this gland stimulating ferment. A new and wonderful field for work is here-with unlocked to those medical practitioners who are conscious of the aims they wish to attain. Not only is normal duodenal dependent upon normal gastric digestion, but normal gastric digestion is in turn dependent upon normal buccal or oral digestion. What an admirable mutual interdependence, correlation and interaction, illustrating in a most subtle scientific way Shakespeare's saying:

"May good digestion wait on appetite, and health on both."

Therefore if we are desirous of having a normal intestinal digestion let us above all things see that the mouth and the stomach are in good condition.

It will be impossible within the limits of this report to dwell fully upon all the various conditions which may bring about dystrypsia. I will limit myself to a more especial consideration of

those forms due to qualitative and quantitative abnormalities in the diet. Abnormal digestion may take place either exclusively in the albuminous foods or the carbohydrate foods. If there is a qualitative unhygienic mixture of the diet, causing an excess of the carbohydrates, a most frequent form, the various bacteria and fungi will cause an excessive fermentation of the carbohydrates with the formation of organic acids, particularly of acetic and lactic acids. This organic acidity of the duodenal and jejunal chyme may become so great that the action of the digestive juices, the pancreatic juice and the bile, will be interfered with, for especially the pancreatic juice requires a certain degree of alkalinity for its action. I have in previous publications advocated the restriction of the word "fermentation" to the bacterial decomposition of the carbohydrates, and the limitation of the word "putrefaction" to the bacterial decomposition of the proteid and albuminous food. (See "Diseases of the Intestines," Hemmeter, Vol. I.) This form of intestinal fermentation of the carbohydrates is one of the most frequent causes of infantile diarrheas, in which there is in many cases no material change in the mucosa of the intestine; and it may give rise to certain characteristic symptoms, which have hitherto been most carefully studied in children. Most prominent among these symptoms are diarrheic discharges, anorexia, acid eructations, and vomiting of acid masses. The abnormal peristalsis is due to the irritations by the excessive organic acid, especially acetic acid. The fermentation begins in the jejunum, and the hyperperistalsis begins there also. Successive parts of the small intestine are involved in the hyperperistalsis, and consequently the jejunal contents are hurried through the entire small intestine with a great velocity.

When such an attack of fermentative dystrypsia begins, the first evacuations represent the contents of the lower bowel, and as a rule presents nothing characteristic, but these first stools once evacuated, the following stools are highly characteristic and have given the whole clinical picture the name of *jejunal diarrhea*. The recognition of these stools depends upon our familiarity with the condition of the normal jejunal chyme. We will have to bear in mind that the contents of the jejunum are normally very rich in mucin, and that the jejunal chyme is physiologically gelatinous as if a thick, tough, glassy liquid had been stirred into the macerated food. Inasmuch as an abundant presence of mucus in the stool is correctly attributable to pathologic catarrhal changes in the intestinal wall, we are compelled to seek for other evidence to decide between what is (1) a jejunal stool with its physiologic admixture of mucus, simply present in that apparently abnormal amount because it is rapidly hurried through the entire intestinal canal, and (2) what may be a catarrhal stool dependent upon enteritis. The distinguishing features for a catarrhal stool are the presence of epithelia and round cells derived from the mucous membrane which are absent in the jejunal stool. The jejunal stool is very rich in bile pigment, has only a slight fecal odor, is generally of an acid reaction. By these features it will be possible to distinguish between the jejunal and the catarrhal stool. The dystrypsia due to carbohydrate fermentation which thus gives rise to the jejunal diarrhea, is important also because in adults as well as in children it may eventuate in actual catarrh of the mucosa or enteritis. The anamnesis indicating an excessive carbohydrate ingestion, and the examination of the stools showing unusual amounts of undigested starch by Lugol's solution, will clinch the



diagnosis. In my laboratory starch is at times not found by Lugol's solution, not even in abnormal stools, where we would expect to find it. I cannot believe that the starch is digested in such cases, but think it is decomposed by fermentation for the fermentative products of starch are abundantly present in such stools. Van Ledden Hülsebosch (*Makro. u. mikroskopische Diagnostik der menschlichen Excremente*, 1899), however, claims to have found starch in his stools, within and without starch-containing plant cells every time he ate potatoes. Nothnagel's experience led him to look upon the presence of starch in isolated granules as well as in fragments, in the feces as pathologic if these could be found quite abundantly.

It is therefore not an easy matter to decide between what is normal and abnormal quantitatively and qualitatively concerning the presence of starch in the feces. Unfortunately for the exactness of their observations, Hülsebosch and others did not state how much starch was ingested when they observed it in the feces. Evidently starch diet can in the normal individual be so far augmented as to make undigested starch appear in the feces. Then again, the process of cooking will have a marked influence on this phenomenon. Raw or only partially cooked starch will leave a greater undigested residue than boiled starch. We have no right to expect the intestines of the human being to digest raw starch completely. Starch occurring within cellulose membranes has no diagnostic importance. Only the starch which occurs in isolated paste-like residues is significant. In the normal individual no or very few such isolated starch residues can be found on a diet containing a medium amount of carbohydrates. If such residues are abundant—they signify an intestinal disturbance



—and it is a well-known fact that such residues are not abundant except in stools of a thin consistence, this in itself pointing to an abnormality. The seat of such starch dystrypsia is the small intestine—for the stomach and colon are not directly and actively concerned in amyolysis. And as starch is the most readily digestible substance in our diet the appearance of an abundance of starch residues in the stool, as a rule, points to a severe digestive disorder, if the cases are chronic, the acute fermentative dystrypsia of adults excepted. In chronic persistent cases it is my custom to exclude all starch from the diet and in re-allowing it to grant only such amounts as will be completely digested, as shown by fermentative test of feces and staining with Lugol's solution of iodine. If the feces give a marked primary fermentation, according to Adolf Schmidt's test, I exclude starch. Such is my custom based on an abundant experience and it has never caused me to regret the restriction. I do not, by this admission of the value of Schmidt's fermentation, desire to be understood that I accept his method as infallible, but I do not believe that the feces should normally give an intense, immediate fermentation, for this is due either to carbohydrates or to their products. Microscopical examination of stained preparations of the feces will permit of reliable deductions, and this method is more applicable to practice. Normally Lugol's solution should show no blue color in the stool.

*Remnants of Meat Fibers.*—An abundance of undigested muscle fibers after a weighed test diet (See Ad. Schmidt u. J. Strasburger, *Die Faeces des Menschen*, S. 4 and 5) is always significant of abnormal intestinal digestion and if the nuclei in the muscle fibers are very evident it signifies abnormality of the secretion of the pancreas (insufficiency of the pancreas). The treatment

of course will in the first place have to regard the diet, for in the great majority of such cases as a rule nothing further is necessary. Similarly if the dystrypsia is due to excessive proteid ingestion, an exclusion of this class of foods will be necessary. But a decision to which of these two classes the dystrypsia is assignable is not always to be arrived at promptly and surely. Here clinical experience and macroscopic and microscopic examination of the feces are telling factors. In either case total abstention from food is one of the most effective means of treatment, especially if it follows an evacuation of the entire intestinal canal effected by the old and established remedies, of which there are still none more practical than calomel and castor oil. I have rarely found intestinal disinfection necessary in such cases, if the diet regulations were faithfully carried out.

So the presence of an abnormal amount of muscle fibers in the stool indicates a disturbance of intestinal digestion in the broadest sense, it does not enable us to precisely define the character of this intestinal dystrypsia, or to localize it. If the nuclei are well preserved in the muscle fibers found in the stool, we are justified in the conclusion that the function of the pancreas is insufficient, because the pancreatic secretion is the only one which can digest the nuclei of muscle fibers, but extensive putrefactive processes in the colon can also effect nuclear solution. Therefore it is only the positive finding of preserved nuclei that permits of an exact deduction.

*Presence of Connective Tissue.*—As the pancreatic secretion is incapable of digesting the connective tissue in unboiled meat, the presence of an excessive amount of undigested connective tissue fibers when scraped raw beef has been eaten, justifies us in the conclusion that the gastric digestion

is imperfect. Therefore the presence of an excessive amount of connective tissue points to abnormal gastric digestion, and not to an intestinal disturbance.

*Fat.*—The appearance of droplets of neutral fat and of fatty crystals is pathological, but the appearance of fat in form of soaps has no diagnostic significance.

We have therefore in the preceding abstracted the diagnostic significance of the appearance of starch, muscle fiber, connective tissue fibers, fats, fatty acids and soaps, in the feces, and these comprise practically all food remains that permit of diagnostic deductions.

*Treatment.*—(1) The diet. In the author's experience it is impossible to succeed with a radical enforcing of strict diet of any kind, but it is wise to recommend what is known as a bland diet; above all things, to study the stools, if possible by the microscope and stool-sieve, in order to discover what foods pass the intestinal tract undigested. These must, thereupon, be avoided, or given in so finely divided a state and in such small quantities that their digestion becomes easier. It is also of importance to utilize the observations which the patients have made upon themselves with regard to the diet. They frequently know what causes distress and what can be digested. The stool examination, however, will guard against deception. The author makes it a rule to forbid alcohol, tea, coffee, and tobacco to these patients. In great exhaustion he allows small quantities of a superior wine or whisky, under strictest control. In some patients a diet rich in carbohydrates, in others one rich in proteids (beef, fowl, fish), is well digested. In fact the diet to be followed can not be decided until a dietetic experiment is made. (2) The same holds good with regard to

the treatment of the constipation. Here the practitioner will have to decide whether this is due to atony or spasm of the intestinal musculature, for what will benefit one condition will harm the other. Here, also, in most cases, a therapeutic experiment will be necessary before we can discover whether we are confronted with atony or spasm. The majority of these patients require exercise after meals. A few that are weak may require rest in bed. Especial attention must be paid in the selection of the food for the last meal of the day. Great moderation in the amount eaten and the digestibility are the most important points to bear in mind. A heavy supper will often produce a restless night. (3) The treatment of the general neurasthenia will be that by electricity, hydrotherapy, massage and baths. Insomnia demands attention and often yields to efforts directed to cleaning the colon and stomach. Hypnotics must be avoided as long as possible.

Whenever a dyspepsia has existed for a considerable time on a purely functional basis, it may eventuate in a disease with definite anatomical alterations. One of the most common symptoms is augmented intestinal peristalsis as a result of irritation by fermentative masses. A condition results in which the contents of the upper part of the bowel are hurried through the entire intestine in an unaltered condition—*i.e.*, the stools may present the same properties as are characteristic of the contents of the jejunum, which are normally thick, but liquid and gelatinous. When there is excessive bacterial activity, the various intestinal antiseptics have been advocated. Personally the author has been able to get along without them in the great majority of cases. He has seen very grave results follow the administration of the irritant antiseptics. Perhaps the most available are bismuth salicylate and subgallate,

betanaphthol bismuth, thymol, menthol, resorcin and salol. Creosote, even in small doses, has, in the author's experience, deranged the stomach in sufferers from dystrypsias. In cases in which the gastric secretion of HCl was suppressed, he made a trial with the orexin so strongly recommended by Penzoldt, and noted in three cases an irritative diarrhea which became manifest after the first two doses, and ceased when the remedy was discontinued.

The following formulas have been used in a large number of cases by the author, for the special symptoms of intestinal dystrypsia.

The first one has proved useful in the putrefactive diarrheas, especially when associated with abdominal pain :

R	Tannigen .....	4.00 gm.	(1 dram)
	Bismuth subgallate..	8.00 "	(2 drams)
	Salol .....	1.55 "	(24 grains)
	Denarcotized extract		
	of opium.....	0.20 "	(3 grains).

This can either be made into twelve capsules or prescribed with six ounces of some elixir, of which the author prefers the elixir of gentian and the essence of calisaya (P. D. & Co.), three ounces of each, in doses of a tablespoonful three or four times a day.

The author's favorite recipe for anorexia from gastric hypochylia in intestinal dystrypsia is the following :

R	Strychnine sulph. ...	0.02 gm.	( $\frac{1}{3}$ grain)
	Dil. hydrochloric acid	15.00 "	( $\frac{1}{2}$ ounce)
	Fluid ext. condurango	45.00 "	( $1\frac{1}{2}$ ounces)
	Elixir of gentian....	180.00 "	(6 ounces).

M. Sig.: One-half of a fluidounce in two ounces of water, one-half hour before meals, through a glass tube.



The dilute HCl cannot be given in sufficiently large quantity to completely replace the normal secretion if this is absent entirely. Its function is merely that of a gastric and pancreatic stimulant in these doses.

Or:

- R Tinct. of nux vom. . . 9.30 grm. (2½ drams)  
 Essentiæ calisayæ (P.  
 D. & Co.) . . . . . 60.00 " (2 ounces)  
 Elixir of gentian. . . 180.00 " (6 ounces).

M. Sig.: One-half of a fluid ounce thrice daily, one-half hour before meals.

When there are evidences of anemia with the gastric hypochylia, the following acts satisfactorily:

- R Quin. sulph. . . . . 1.16 gm. (18 grains)  
 Strychnine sulph. . . . 0.02 " (⅓ grain)  
 Sulphate of iron. . . . 0.80 " (12 grains)  
 Arsenious acid. . . . . 0.012 " (⅓ grain).

M. Sig.: Make into twelve pills. One pill three times daily. They must be prepared fresh and not coated.

Boas uses the following powder for anorexia:

- R Ext. of nux vom. . . . 0.024 gm. (⅔ grain)  
 Bismuth subcarbon. . . 0.520 " (8 grains).

M. Sig.: Make twenty powders. One powder three times daily.

Menche has warmly recommended resorcin sublimate, and it undeniably improves the appetite in cases of incipient gastric and intestinal fermentation. It has also a slight sedative action. The following is Menche's formula:

- R Resorcin resub. . . . . 2 gm. (30 grains)  
 Tinct. of rhubarb. . . . 15 c.c. (½ ounce)  
 Simple elixir, enough to  
 make . . . . . 90 " (3 ounces).

M. Sig.: A tablespoonful twice daily.



Resorcin can also be advantageously combined with bismuth salicylate, salol, and betanaphthol in the following manner :

℞ Resorcin resub..... 5 gm. (75 grains)  
 Bismuth salicylate,  
 Powdered rhubarb,  
 Sodium sulphate, of each 10 " (150 grains)  
 Milk-sugar ..... 15 " (225 grains).

M. Sig.: An even teaspoonful twice to three times daily.

If dyspeptic diarrhea is present the rhubarb and sodium sulphate must be replaced by calcium phosphate and calcium carbonate, of each 25 grams.

The following formulas are recommended by Ewald for anorexia with fermentation :

℞ Tinct. of nux vom.. 22.56 gm. (6 drams)  
 Resorcin resub..... 5.40 " (83 grains)  
 Tinct. amar. .... 11.25 " (3 drams).

M. Sig.: Take ten to fifteen drops every two hours.

℞ Fluid ext. condurango 17.00 gm. (4½ drams)  
 Resorcin resub..... 4.00 " (1 dram)

M. Sig.: Thirty drops four times daily.

In all cases of intestinal dyspepsia the aim must be to understand the cause and remove it. Not to give medicines except as an "ultima ratio."



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*Concerning the Role of Intracellular Catalytic Processes in the Pathogenesis of Malignant Neoplasms.*

BY

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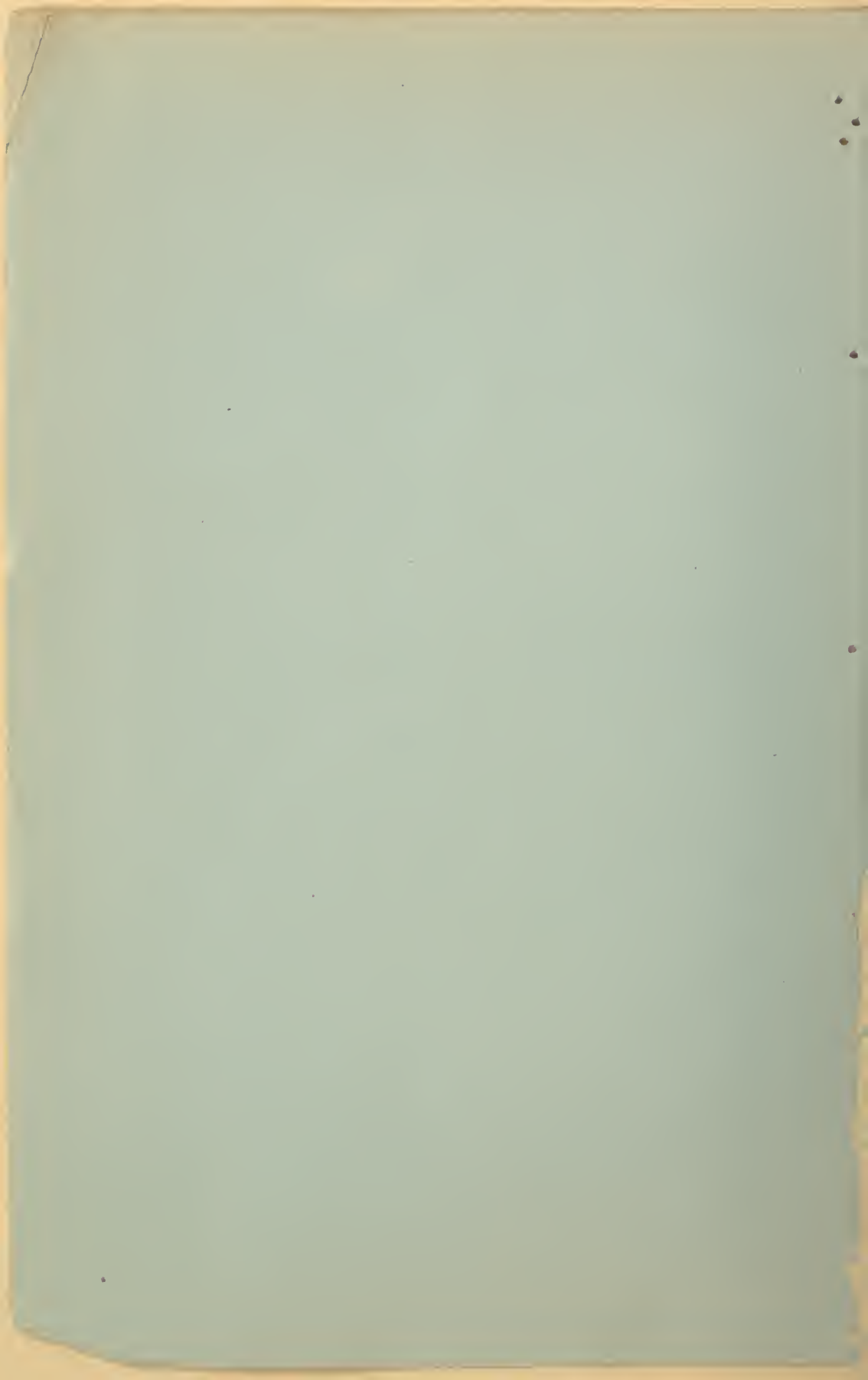
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FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,

APRIL, 1903.



CONCERNING THE ROLE OF INTRACELLULAR CATALYTIC  
PROCESSES IN THE PATHOGENESIS OF MALIGNANT  
NEOPLASMS.

BY JOHN C. HEMMETER, M.D., PH.D.,  
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IT is now accepted as one of the truths of physiology, as well as pathology, that the cells of the mammalian organism may change their form, and even at times their structure, during their existence. Physiologically, they may change their forms under the influence of age, and according to many extrinsic and intrinsic influences to which they are subjected. It is often impossible to draw sharp lines of demarcation between that which is normal and that which is abnormal in such changes. Virchow expressed himself in the words that in reality there is no distinct line of demarcation between "physiological and pathological processes, and that the latter are only physiological processes which take place under difficult conditions." Cancer pathogenesis may accordingly be looked upon, in part at least, as a problem of growth of cells under difficult conditions, and in that case we have a right to expect that the solution of this problem may be aided by the adaptation and application of recent discoveries in physical chemistry to the pathology of cell growth, just as physical chemistry by its revelations concerning osmosis and the ionic theory has thrown light upon normal cell growth.

We have learned to look upon the individual cell as representing in itself a highly complicated system of organized parts, the latter standing in most intimate co-relation with each other. The cell may be conceived as representing on a small scale that which the entire cell state is on a grand scale, *i. e.*, a unity, a specific system of organized parts. Shall we seek the cause of malignant neoplasms, conditions of cell anarchy, caricatures of normal developmental processes, within or without the cell? This question separates all hypotheses concerning the etiology of malignant neoplasms into two great groups:

First, those assigning the cause of cancer to qualities inherent in the cells themselves. Secondly, those assigning the etiology of cancer to the action of some extraneous poison, particularly to the influence of micro-organisms. Although the latter theory may logically include the effect of toxins, even those not of bacterial origin, these two great



groups may be concisely designated as, first, the histogenetic, and second, the parasitic theory, on the origin of cancer.

It is not my intention to discuss in this report the relative merits and demerits of these two groups of hypotheses. These matters are set forth in the various works on pathology, but most forcibly, perhaps, in the work of Professor David von Hansemann, *Die Mikroskopische Diagnose der Bosartigen Geschwülste*. Also in the work by Lubarsch, *Zur Lehre von den Geschwülsten*, in Ribbert's work, *Lehrbuch der allgemeinen Pathologie*, and in various editions of Lubarsch and Ostertag's *Ergebnisse d. Pathologie*. Hansemann, Ribbert, and Lubarsch are opposed to the parasitic theory, and by far the greater number of prominent German pathologists, while they are non-committal, have not given support to it. Recent American research work by R. B. Greenough, and Edward H. Nichols, published under the auspices of the Harvard University Cancer Commission, in the *Journal of Medical Research*, 1902, vol. ii., invalidate the parasitic theory. On the other hand, the histogenetic theories, as examples of which we may mention those of Thiersch, "Der epithelial Krebs," Leipzig, 1865; Cohnheim, (*Allgemeine Pathologie*, Bd. i., S. 723) and Ribbert (l. c.) have the advantage that they cannot be controverted at all, being hypotheses pure and simple, without experimental foundation, so that they cannot be tested experimentally. The only excuse for the formulation of an hypothesis is that it gives the incentive to experimental investigation, and the formulation of inquiries into the nature of the thing discussed; and an hypothesis that does not permit of this has thrown no light on the subject to be solved, but simply side-tracked it. Thiersch conceived that the connective tissue might become weakened by disease or old age, and thereafter the epithelial tissues gain the supremacy and penetrate into the depths of other tissues. This theory does not explain the occurrence of cancer in young people, and cannot be tested experimentally.

Cohnheim conceived the cause of malignant neoplasms to be the supposed existence of congenital embryonal cells, which have remained latent in different tissues of the body. This theory does not explain why such undifferentiated embryonal cells, if they really occur, should suddenly begin to proliferate in an unrestricted manner.

This theory of Cohnheim has not become more probable by the discovery of unutilized segmentation cells of the frog by Roux,<sup>1</sup> who observed that in this animal, cells occurred which were not utilized, and were surrounded by growths of other cells. Barfurth observed the disruption and subsequent continued growth of a segmented portion of the exoderm. With regard to the mixed tumors it is very probable, however, that they can arise from disrupted embryonal germinal cells. Ribbert

<sup>1</sup> Anatomisches Heft, I. Abth., Heft 9.

is of the opinion that this is particularly the case in sarcomas occurring in the very young.<sup>1</sup> Many of the tumors, particularly malignant tumors (glioma, teratoma, myosarcoma), would receive a satisfactory explanation of their histogenesis from the assumption that they grow from pre-existing dislodged embryonal cells. This is particularly true of tumors like carcinoma of the kidney developed from dislodged portions of the adrenal bodies. Ribbert assumes that these grow from portions of the adrenals which have been disrupted in an embryological state and continued to live in the substance of the kidneys. Such embryonal germinal cells may remain quiescent in the kidney parenchyma without forming a tumor, but under certain conditions which are not as yet thoroughly understood (Ribbert mentions hyperæmia), such cells undergo a rapid and progressive growth and multiplication. At first this is apparently a benign growth; it is well circumscribed and limited. But when it strikes a vessel and causes its wall to atrophy by pressure, it proliferates into the vascular lumen and may even cause metastases. The important point to bear in mind in the case of this tumor is that there are precursory stages which are not carcinomatous, and that they may persist in this benign state indefinitely. Evidently some additional tumor producing agency is necessary here to convert the benign growth from dislodgement of adrenal cells into the parenchyma of the kidney into a malignant growth. It shall be our duty in the following to approach a solution of this question, whether or not an additional tumor producing agency is necessary to impart the character of malignancy to cells already in a state of proliferation.

*Metaplasia.* The transformations in form and structure which cells may undergo are important for the understanding of normal and pathological cell growth. Evidently if cells can change their specific structure and replace it by a different structure, which is, however, definitely differentiated or undifferentiated, it is not necessary to assume with Ribbert, that in all cases of mixed tumors we are dealing with disrupted or dislodged embryonal cells, as the starting point. Lubarsch's study of metaplasia suggests the possibility of the derivation of such tumors from metaplastic cells.

The supposed participation of muscle, liver, cartilage and lymph gland cells in the architecture of carcinoma metastases<sup>2</sup> are not genuine metaplasia—*i. e.*, transformation meaning the replacement of specific cell or tissue structure by other definitely differentiated structure of the same kind of tissue, but they represent what Lubarsch calls pseudo-metaplasia, *i. e.*, the histological "cell accommodations" and "variations" of Hanseemann—these are mere changes of form, not of structure. Naturally if the

<sup>1</sup> Loc. cit., p. 606.

<sup>2</sup> Rindfleisch, Klebs, Gussenbauer, von Leyden, XX. Verhandl. d. Congress f. i. Med.

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actual participation of the liver cells, etc., in carcinoma metastases derived from an original growth the stomach could be demonstrated, it would be a point gained for the advocates of the theory of infection for malignant neoplasms, but thus far their observations are cases of pseudo-metaplasia.

Lubarsch distinguishes three types of cell changes :

1. Pseudo-metaplasia—change in form but not of structure.
2. Metaplasia—structure transformation—replacement of specific cell or tissue structure by the different kinds of structure, but which is definitely differentiated and derived from the same type of tissue.
3. Undifferentiation—transformation of definitely differentiated cells into undifferentiated. Of this there are two types :

(a) Transient or physiological undifferentiation, occurring during progress of indirect cell division, during which typical structure is temporarily dissolved.

(b) Pathological (permanent) undifferentiation which always leads to death of cells by degeneration or atrophy.<sup>1</sup>

Ribbert seeks the cause of carcinoma in an inflammatory proliferation, which disrupts the cell from its physiological connection. The cause of the unrestricted growth of the cell is the removal of resistance to growth in the environment caused by the inflammation. This theory does not explain why a carcinoma does not occur in every instance where an inflammation disrupts cells from their normal environment, and why carcinomas actually develop in the absence of every evidence of inflammation. It is seen that all of these theories have some resemblance. They all attribute the malignant neoplasm to some undefined power of growth within the cell and differ only in regard to the reasons assigned to this power of growth.

A fourth theory, which is that of Hansemann, does not concern the etiology of malignant neoplasms, but only their morphology and physiology. His conception is expressed in the word "anaplasia." Hansemann first used the word "anaplasia" in 1890,<sup>2</sup> from *ἀνα*, backward, and *πλασσειν*, to build. He understands by it a condition in which cells have lost in part their specificity, have become "entdifferentzirt," so that they have acquired the property of independent existence, have lost what he calls "altruismus." He conceives that this anaplasia is brought about by abnormal, especially unsymmetrical, mitoses, and that some of the "idioplasm"<sup>3</sup> is thereby lost, while

<sup>1</sup> Benecke's "Kataplasia"—Hansemann's "Anaplasia." For fuller account see O. Lubarsch, Arbeiten a. d. Anat. Abtheilung, d. kgl. Hyg. Instit., Posen, S. 209, 1901.

<sup>2</sup> Virchow's Archiv., Bd. cxiv., p. 321.

<sup>3</sup> Idioplasm. In biology, a term introduced by Nägeli for a special hereditary reproductive substance not contained in the body of the cell, but in the chromosomes of the nucleus, controlling and determining the actual characters of the particular cell, and also those of all its descendants. Each idioplasm is composed of several or many *ids*, which are capable of growth



idioplasm which had previously been in the background now comes to the front.

#### DIFFICULTIES IN THE WAY OF THE PARASITIC THEORY OF CANCER.

Above all we must recollect that the controlling histological elements in carcinomas are the connective tissue and the epithelial cells. These cells are the element which cause the tumor by their multiplication and advancement, and generate the metastases by their proliferation in other organs. We do not find such a phenomenon in the parasitic diseases. In all parasitic diseases it is the micro-organisms which transfer the diseases and then make a new inflammatory focus out of the elements and cells of the newly infected organ. In a parasitic disease the tissues of the newly infected organ itself compose the inflammatory tumor. In cancer the cells of the secondarily infected organ never participate in the metastasis, but this is composed exclusively of the cells of the organ primarily diseased. A primary cylindrical carcinoma of the stomach, when it causes a metastasis in the liver, never infects the cells of the liver, but the metastasis is composed of cylindrical stomach cells, or glandular epithelium from the mucosa of the stomach. This is true of other metastases. In no infectious disease do we find that cells from the primary focus of inflammation are driven about, nor do such cells of infectious diseases cause characteristic new-growths histologically like themselves in other organs.

1. The parasites must live within the cell, and yet not injure it, in order to make the parasitic theory harmonize with the well-ascertained morphological facts concerning cancer proliferation. We must assume, then, a kind of symbiosis of parasite and cell. At the same time they must be able to bring into disorder the various finer cell parts already considered, in order that the incentive to cell proliferation shall be present. Whether such parasiticism is possible is doubtful.

2. As the unrestricted proliferation of the cells, as well as the power to form metastases, is ascribed to the presence of the parasites within the cells, it is necessary to assume that every cell contains a parasite, and that the parasite multiplies as rapidly as the cell, in order that each new cell shall receive its parasite. If the parasites do not divide in the identical moment that the cell divides, cells will eventually arise which contain no parasites, and, therefore, have no abnormal properties in the sense of the adherents of this theory. This condition necessitates that the cycle of development of the parasite should coincide with the rate of multiplication of the proliferating cells.

3. The best evidence points to the conclusion that transplantation of

and multiplication by division; although much smaller in bulk than the rest of the living substance of the cell or body (trophoplasm), idioplasm is the active element in the process of formation, and determines the detailed construction of the trophoplasm, which is the passive element.

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malignant neoplasms is successful only among animals of the same species. A parasitic disease, however, if we are permitted to draw inferences from the well-known infectious diseases, should be transferable from one species to another.

4. Primary carcinomas rarely occur in multiples; only in exceptional cases of epithelioma of the skin has this been reported. Typical congenital malignant neoplasms (rhabdo-myosarcoma of the kidney, glioma of the retina) have been reported in children whose parents were not affected with malignant neoplasms.

5. The cells of organs invaded by cancerous metastases do not participate in the secondary growths. The metastases, with few exceptions, represent the cell type of the mother carcinoma.

6. Cells of a different type, then, being only exceptionally involved in the metastases, it is necessary to assume that every kind of cancer must have a special species of cancer parasite, which would not be capable of causing cells of another type to proliferate in a cancerous manner. A pavement epithelial cell of the œsophagus, for instance, when it causes a metastasis in the stomach, produces a neoplasm composed of pavement epithelium; never cylindrical cell growth or an adenocarcinoma—structures which are found in the normal gastric mucosa.

ATTEMPTS AT EXPERIMENTAL PRODUCTION OF CARCINOMA. The special object of this report is to communicate in abstract a series of researches or efforts aiming at an experimental production of carcinoma of the stomach. This organ is more than all other organs in the body fitted for a study of cancer because it is more frequently invaded by this disease than any other organ or tissue in the body.<sup>1</sup> Not only this, but it is the only organ of which it is definitely known that a benign lesion, the peptic or gastric ulcer, may exist as such for months or even years and then can undergo changes transforming it into a typical malignant neoplasm. The scientific value of any series of investigations on cancer will depend very much upon the experience and familiarity of the investigation with the architecture and pathological physiology of these growths. It is for this reason chiefly that I confined my experimental studies to the adenocarcinoma of the stomach, believing that I could not be misled in confusing this characteristic growth with any of the other neoplasms of the stomach, or with simple inflammatory tumor. (See Hemmeter, *Diseases of the Stomach*, 3d edition, p. 527 to 586, on "Malignant Tumors of the Stomach.")

Gastric carcinoma may develop from the oxyntic or parietal cells (gland cells) of the peptic ducts, when they constitute the adenocarcinomas; but they may also arise from the cylindrical epithelium of the vestibules, and then they are termed cylindrical cell carcinomas; and finally,

<sup>1</sup> The literature and statistics on this subject will be found compiled in a volume by Behla, "Die Carcinomlitteratur" (up to 1900), pages 244 and 248.

they may develop from the mucous glands; if the adenocarcinoma is restricted to the mucosa and grows outward, the stroma is composed of newly-formed connective tissue—if the carcinoma grows in the main muscular layer the stroma may be muscular tissue.

In 1898 I began with experiments attempting the transplantation of pieces of adenocarcinoma from the human stomach into the stomachs of dogs, cats, and guinea-pigs. I have a record of forty-two such attempts, but in not one case have I succeeded in successfully transplanting a piece of human cancer of the stomach into the stomachs of any of these animals.<sup>1</sup>

In the *Journal of Medical Research*, vol. vi., No. 1, and vol. viii., No. 1, Dr. Leo Loeb describes the transplantation of tumors (sarcoma) through forty generations respectively of rats of different age and sex. In all cases a sarcoma was produced, and the details of the growth and generative changes of the cells were preserved. Even certain limits of variability in the cells were also preserved. Dr. Loeb assumes it to be a well-known fact that transplantation of cells<sup>2</sup> into animals of different species are usually unsuccessful, and this may account for the impossibility of producing a tumor in another species. The sarcoma which he found in the connective tissue of the parathyroid could never be successfully transplanted into any other species of animals. Guinea-pigs, animals so susceptible to tuberculosis of different origin, remained absolutely unaffected by these tumors. He suggests that certainly none of the ordinary micro-organisms can be the cause of these new-growths, of which there was no doubt that they were true sarcomata.<sup>3</sup>

In a more recent contribution, Mayet<sup>4</sup> reports transplantation experiments, in which he introduced pieces of human cancer into animals subcutaneously, or by rubbing up pieces of human carcinoma with sterile bouillon, and injected the resulting emulsion into the peritoneal cavity, or into the circulation of animals. Most frequently, however, he injected a glycerin extract of human cancer tissue, aseptically macerated, or a filtrate obtained by filtering such crushed tissue through a Pasteur filter or an asbestos filter. Previously, the animals used received cantharidin injections, with which he aimed to produce transitory nephritis and so to predispose the kidneys to the development of cancer nodules. Mayet experimented on dogs, rabbits, and white rats.

<sup>1</sup> The literature on transplantation of cancer from man to animals is compiled in "Ueber die Aetiologie des Carcinoms," by Gustav Fütterer, Wiesbaden, 1901. It appears from this compilation that 11 experimenters claimed to have had successful transplantations, but 19 others had negative results. A number of other transplantations are mentioned and criticised in Hanseemann's work, loc. cit., p. 174.

<sup>2</sup> The literature on the transplantation of cancer cells from animals to animals is compiled in the work of Fütterer, Behla, Hanseemann.

<sup>3</sup> Loc. cit., p. 49.

<sup>4</sup> "Production du Cancer chez les Rats blancs Introduction dans leurs Economies des Substances constituantes des Tumeurs malignes de l'Homme?" *Gaz. hebdom. de Medic. et de Chir.*, January 19, 1902, No. 6, p. 64.



He admits that his experiments on dogs and rabbits were unsuccessful, but claims that he succeeded in certainly producing cancer lesions in three white rats out of fifty-three of these animals experimented upon. These alleged successful cases he claimed were produced by the glycerin extracts or filtrates from human carcinoma. A critical study of Mayet's paper leads one to be especially skeptical concerning his claim of having produced a genuine carcinoma in this manner. He does not describe the typical architecture of a carcinoma, but speaks of epithelial cancerous lesions.

An interesting series of experiments on tumor transplantations and inoculation is described by Dr. M. Herzog.<sup>1</sup> The original animal which Herzog used was a descendant of the white rat from which L. Loeb<sup>2</sup> derived his sarcoma. The growth was a vascular cystic sarcoma of the thyroid in a rat. Over fifty successful transplantations were made in the same species of animal, and these extended over eight tumor generations. In the inoculation experiment of Herzog, pieces of non-infected sarcoma were ground up in a sterile mortar with sterile quartz sand and silicon powder. The tissues were ground up with physiological salt solution—the emulsion so prepared filtered through a Pasteur filter, and the filtrate so prepared inoculated into culture tubes, showing it to be free from micro-organisms. Several cubic centimetres of this filtrate were injected into the abdominal cavity of rats—not a single one of the rats so treated developed a tumor. Some were killed and examined, and the findings were absolutely negative. Thus far Herzog's investigations are clear and instructive; but further on he mentions the possibility of ultra-microscopic organisms, too small to be seen even by the aid of our best optical instruments. He claims that bovine pest can be propagated by filtrate through a Pasteur filter, and that the work of Nicolle and Abdil Beyer gives evidence that the cause of this disease must be a living organism which can pass through a Pasteur filter. I am not sure that the work of Nicolle and Abdil Beyer justifies such a conclusion.<sup>3</sup>

I have given these previous experiments such detail because they express in the work and words of others much of the work and experiment which I have made personally, yet never published. I have also prepared a sterile filtrate of human carcinoma of the stomach, exactly in the manner as described by Herzog, and injected it into the stomach tissue of dogs, cats, and rabbits, but never succeeded in causing a gastric malignant neoplasm in these animals by this process.

It is a well known fact of pathology that the human gastric or peptic ulcer may become transformed into an adenocarcinoma, apparently

<sup>1</sup> Journal of Medical Research, vol. viii., No. 1, p. 74.

<sup>2</sup> Loc. cit.

<sup>3</sup> As far as I know the experiments of L. Loeb and M. Herzog have not been confirmed by others, nor am I in a position to judge whether the neoplasms they claim to have produced were genuine sarcomas.

spontaneously. This process has been described in a classical investigation by Hauser.<sup>1</sup>

In 1900 I paid a visit to Professor Hauser's laboratory at the University of Erlangen, and was fortunate enough to see some of his original preparations and sections. I have also had a rather exceptional clinical experience with cases of gastric ulcer in the human being, which I had studied, in one case, for over two years, during which it presented the typical clinical history of gastric ulcer. Then followed the clinical history of gastric carcinoma and death.<sup>2</sup> Naturally, the question arose in my mind, "*If gastric ulcers could be produced experimentally in animals, their transition into possible adenocarcinoma might be studied at will, or the transformation into adenocarcinoma might be attempted by the transplantation of malignant neoplasms derived from other animals of the same species, or by the injection of sterilized filtrate of ground-up adenocarcinoma of other animals of the same species into the tissues surrounding the edge of the ulcer.*"

Among the causes that are definitely ascertained as contributing to the bringing about of gastric ulcer are especially three:<sup>3</sup> first, impaired vitality or injury to the mucosa of the stomach; second, hyperacidity or supersecretion of gastric juice containing an excess of HCl, and proteolytic ferments; third, an altered or impaired state of the blood.

All three of these factors may be produced artificially, and when we do produce them in the laboratory on animals, peptic ulcers arise in such a large proportion of the animals thus experimented upon, that we have a right to conclude that they are directly attributable to the method pursued. When I speak of peptic gastric ulcer I mean the typical "*chronische Magengeschwür*" as described by Hauser. For defects can be produced in the dog's stomach, for instance (and the literature on the experimental production of gastric ulcer proves this conclusively), which are not true gastric ulcers, but simply ulcerating lesions, which heal rapidly. Gustav Fütterer has produced such lesions by applying to the stomach caustics, ligating the gastric arteries, cutting off the supply of nutrition by stitching large portions of the mucosa with catgut sutures. Defects resulted, but they all healed in a short time. Even when one-third of the quantity of the animal's blood was withdrawn such defects had healed in two weeks. In 1896 Silbermann<sup>4</sup> produced gastric ulcers in dogs by either tying the gastric arteries or causing emboli in them by injecting suspensions of lead chromate.

<sup>1</sup> Das chronische Magengeschwür, sein Verharbungs-Process und die Beziehung zur Entwicklung des Magencarcinoms," Leipzig, 1883; and "Das Cylinderepithelcarcinom des Magens und des Dickdarms, Jena, 1890. See, also, New York Medical Record, 1897, vol. lli, p. 365; also, Hemmeter, "Diseases of the Stomach," third edition, p. 560.

<sup>2</sup> See Hemmeter, New York Medical Record, 1897.

<sup>3</sup> See Hemmeter's "Diseases of the Stomach," third edition, p. 491.

<sup>4</sup> Experimentelles in klinisches zur Lehre von Ulcers Ventriculi rotundum. Deutsch. med. Wochenschr., 1886, No. 29, p. 497.

Thereafter he injected hæmoglobin and pyrogallie acid. When Fütterer resected the gastric mucosa, as stated before, and made injections of pyrogallie acid, he could confirm Silbermann's results, and produced ulcers of the stomach which in every histological detail corresponded to the chronic gastric ulcer of the human being. By making use of this method employed by Fütterer and Silbermann I was successful in producing experimentally gastric ulcers in one series of experiments; eleven dogs out of thirty operated upon developed typical gastric ulcer.

Now I had a method by which this characteristic lesion could be produced experimentally. The next question was, "Could these lesions be in any way experimentally transformed into adenocarcinoma of the stomach, or could they become transformed into adenocarcinoma spontaneously, as has been definitely known to occur in the human being, and as Fütterer has observed, to occur in a rabbit, in which he had artificially produced a gastric ulcer by the method described?"<sup>1</sup>

Hauser has described a structural characteristic of the adenocarcinoma of the stomach, which had developed on the basis of a gastric ulcer, and which is not observed in ulcerating carcinomas not developed on this basis. This characteristic by which the so-called "ulcus-carcinomatousum" can be recognized, consists in a very peculiar behavior in the fibres of the chief muscular layers of the stomach, and also of the fibres of the muscularis mucosæ. This peculiar behavior of the muscularis consists in an oblique ascension of the fibres of the true muscular layer, and a descension of the fibres of the muscularis mucosa, the fibres of both muscular layers converging toward and fusing into each other in front of the edge of the ulcer, which is here composed mainly of connective tissue. The true muscularis bends upward in continuity, and the border of the ulcer, which is composed of very dense connective tissue, is limited by the lower or peritoneal strata of the turned-up true muscularis.

Another feature of the *ulcus carcinomatousum* is that a section made perpendicularly to the surface of the stomach, and through the entire bed of the ulcer, almost invariably exhibits the general outline of a fish-hook.<sup>2</sup> For the causes which bring about this fish-hook formation,<sup>3</sup> the main reason being that the lower edges of the ulcer near the pylorus are, during the efforts of gastric peristalsis to evacuate the chyme into the duodenum, exposed to the most mechanical irritation, and, accordingly, Fütterer has shown that adenocarcinoma, if it develops from an ulcer, always develops from the lower edge. This location for the devel-

<sup>1</sup> Loc. cit., p. 152.

<sup>2</sup> See Hemmeter, "Diseases of the Stomach," third edition, plate ix., opposite p. 506; also New York Medical Record, loc. cit.

<sup>3</sup> Loc. cit., p. 112.



opment of gastric ulcer had already been emphasized in a publication by Dr. Delano Ames and myself, but it is the merit of Fütterer to have emphasized this point as an etiological factor in the causation of *ulcus carcinomatosum*.

I should add that in repeating the experimental production of gastric ulcer, according to the methods of Silbermann and Fütterer,<sup>1</sup> I not only produced mechanical defects, and injected pyrogallie acid in the method described, but I maintained a very high acidity for free HCl in the gastric chyme of the dog by supplying this acid in his food and also pouring it into his stomach through a soft rubber tube. In February, 1900, I came into the possession of a mongrel fox-terrier, who persistently vomited his food. The vomit contained no free HCl or ferments, and at the autopsy a cancer of the stomach was found near the pylorus. Transplantations with this material were made into the stomachs of other fox-terriers, but I was not successful in producing a gastric carcinoma in any other animals inoculated.<sup>2</sup>

In the meanwhile the publication of Fütterer appeared, and it occurred to me that possibly my failure to successfully transplant canine carcinoma was due to the fact that the stomach of the animal into which the inoculation was made was not in a susceptible condition, and that it must be transformed into such a condition by a previous injury. This previous detriment to the tissue, in order to secure successful transplantation of the tumor, has in the case of rats not been found necessary by Leo Loeb and M. Herzog. I did not succeed in securing another dog affected with carcinoma of the stomach until after I had read Fütterer's work in 1901, and this second dog presented an adenocarcinoma which developed spontaneously at the edges of an experimental gastric ulcer. It presented the behavior of the two layers of the gastric muscularis, as first described by Hauser, had a distinct fish-hook form, and exhibited heterotopia of gastric glands, as first described by Virchow<sup>3</sup> and Hansemann.<sup>4</sup> This gastric cancer reached the size of a walnut, and two metastases were found in the omentum. It was this carcinoma which was used in making a filtrate with which the edges of the peptic ulcer previously produced in other dogs were injected.

It will be seen that these experiments are attended with unusual difficulties in procuring the material, for if we wish to study the effect of extract of adenocarcinoma upon experimentally produced gastric ulcer, we must have two sets of animals: one presenting the cause and

<sup>1</sup> New York Medical Record, September 11, 1897.

<sup>2</sup> Sepsis followed a large proportion of the operations, and I could not secure the aid of a competent surgeon who would do these operations aseptically for me. A sterile extract of part of this canine carcinoma was also made and prepared for inoculation and injections into dogs, in which I expected to cause gastric ulcers. A very small quantity of filtrate (48 c.c.) was thus saved, as the largest part of the tumor had been used for transplantations.

<sup>3</sup> Virchow's Archiv., Bd. 111.

<sup>4</sup> Loc. cit., p. 195.

the other the gastric ulcer. If we should accidentally come across a dog with an adenocarcinoma it would take at least two or three weeks to get a number of other dogs having experimental gastric ulcers. It is a matter of great difficulty to determine in the live animal whether it is really afflicted with gastric cancer, and if the cancer is accidentally found at autopsy in a veterinary school, it rapidly decomposes, and unless kept on ice the canine gastric cancer becomes useless for experiments in two or three days, for bacteria, especially the pus cocci, are great hinderances to successful transplantation, as Loeb<sup>1</sup> has emphasized. We will, therefore, in future, have to depend on cancer tissue gotten from living dogs, or soon after the autopsy, or such cancer tissue produced experimentally by the method of Fütterer, which in my experience only succeeds in one-third of the animals experimented upon.

The adenocarcinoma which developed at the edges of the experimental peptic ulcer was found at a time when I was engaged in producing such ulcers in a series of animals. Eight transplantations of such tumor particles were made into the edges of peptic ulcers of other fox-terriers. Five of these animals died of infection and other intercurrent accidental complications. Three of them lived each three months after the transplantation, and of these three, two had developed adenomatous proliferations closely resembling carcinoma at the edges of the gastric ulcer nearest the pylorus.

**SUMMARY.** Eight dogs afflicted with experimental peptic ulcer, inoculated by injecting tumor particles made of suspension of the tumor cells of a gastric adenocarcinoma into the edges of the gastric ulcer. Five of these animals died of sepsis, etc., three of them lived three months each, developed symptoms of gastric carcinoma, and in two of them the adenomatous proliferations described by Hauser and Fütterer were evident at the pyloric edge.

This method of inoculation by a suspension of the tumor cells was preferred to transferring actual pieces, because I had a very small original tumor to start with, and for the purpose of demonstrating the principle involved, it makes no difference whether we transfer large pieces or only a few cells, for any ensuing development of carcinoma can only in these cases be attributed to a further growth of the injected carcinoma cells, or whatever hypothetic micro-organism or tumor producing agency they may be assumed to carry. My main object, however, was to discover whether the cancer formation at the edges of gastric ulcers could be induced by the injection of a fluid gained from canine carcinoma and free from carcinoma cells as well as micro-organisms, as far as our modern methods of testing these two points permit us to judge.

<sup>1</sup> Loc. cit.

PRODUCTION OF EFFORTS AT ADENOMATOUS PROLIFERATION FROM THE EDGES OF PRE-EXISTING EXPERIMENTAL GASTRIC ULCER BY THE INJECTION OF CELL-FREE AND STERILE EXTRACT OF CANINE GASTRIC ADENOCARCINOMA. The sterile and cell-free extract of canine gastric adenocarcinoma was prepared by grinding up non-infected portions of this cancer in a sterile mortar with quartz sand, together with physiological salt solution. Then this emulsion was filtered through a Pasteur filter, and cultures made upon a number of the most commonly used media, which proved negative. In order to exclude the possible action of bacteria, I might of course have used strong antiseptics in the solution, such as bichloride of mercury, formaldehyde, carbolic acid, etc. There are, however, two grave objections to this way of proceeding. I shall have to premise what I intend to say by stating that I had from previous observations and experiments gained the impression that the tumor producing agency in these cases was not the cell itself, nor a micro-organism, but an enzyme, which had passed through the filter. The first objection to using antiseptics or heat in sterilizing the filtrate was that whilst they no doubt could destroy any micro-organisms, a sufficient degree of heat, as well as the more effective antiseptics, would also destroy any possible enzyme present. The second objection to using these substances was that any possible effect upon transforming the peptic ulcer might have been ascribed to the antiseptic use or to chemical additions to the filtrate and not to any inherent qualities derived from the original tumor. I have, however, shown that thymol, even in saturated solution, has no such destructive action upon the proteolytic ferments of the intestinal canal.<sup>1</sup>

A. S. Loevenhart and Kastle, in their beautiful investigation on the reversibility of the action of lipase<sup>2</sup> and Loevenhart in his researches on lipogenesis<sup>3</sup> toluene was used to keep the tissue extracts sterile, and evidently the effectiveness of lipase was not impaired by this antiseptic. In one of my successful experiments I also made use of toluene, and I believe this excluded the possible action of any bacteria that might be presumed to pass through a Pasteur filter. From the investigations of William G. Wherry<sup>4</sup> concerning the permeability of the Berkefeld and the Pasteur-Chamberland filters to bacteria of small size it seems justifiable to conclude that bacteria of small size can pass through them. The bacillus producing pneumonia in guinea-pigs, for instance, will pass through the pores of a small Berkefeld filter, No. 5,

<sup>1</sup> Hemmeter, "Ce que Deviennent les Ferments Digestifs—Bactéries proteolytique du Colon," XIII. Congres International de Médecine, Paris, 1900, also "Ueber das Vorkommen von Proteolytischen und Amyolytischen Fermenten in Inhalt des Menschlichen Kolens," Pflüger's Archiv. f. die ges. Physiologie, Bd. 81, 1900.

<sup>2</sup> American Chemical Journal, xxiv., 1900.

<sup>3</sup> American Journal Physiol., vol. vi. p. 331.

<sup>4</sup> Journal of Medical Research, November, 1902.



and sometimes organisms which do not pass through the above filters, like the bacillus coli communis, may grow through. Referring once more to the work of Herzog, it seems justifiable to conclude from the results of Wherry, that if the virus of a disease passes through the pores of a Berkefeld filter, it is not necessarily ultramicroscopic. The practical import for our research was that we could not rely exclusively upon filtration, but had to resort to some antiseptic in order to attain an absolutely sterile liquid. For this purpose thymol, and in some cases toluene, were used.

As far as the methods at present at our disposal permit me to judge, the filtrate extract used for these inoculations was sterile. The injection of filtrate into ten animals afflicted with experimental gastric ulcer resulted in four of them in the development of adenomatous proliferation closely resembling an adenocarcinoma at the edges of the ulcer. The time in which the animals were examined after the first injection varied from twelve to fifteen weeks after the first injection. The histological characteristic of the carcinomas developed corresponded closely to those described by Hauser and Fütterer: (1) There was a diffuse proliferation of glands; (2) heterotopia of gland cells; (3) the cells of the proliferated gland ducts stained apparently as deeply as the normal cells in the same section; (4) there were numerous mitoses in the proliferated gland cells, some of them atypic, and also mitoses in the connective tissue cells close to the proliferated glands. Notwithstanding these histological characteristics, I am by no means of the opinion that the proliferation produced in this way was really a malignant neoplasm, for I have observed such proliferations around two peptic ulcers that were excised by operation, and the patients remained well eight and nine years respectively.

The question arises if the adenoma thus produced was not caused by the implantation of a carcinoma cell, nor by infection with bacteria, what did cause it? This question opens a wide field for reflection. If the Pasteur filter can keep bacteria as well as cells from passing through, the incentive to growth can only have been given by some chemical substance capable of passing through the filter, and contained in the filtrate. This substance was extracted from a pre-existing carcinoma in a dog. But it is essential to bear in mind that in one case the gastric ulcer developed into a carcinoma spontaneously. Evidently the cellular tissue of the stomach, in its abnormal condition, is capable of producing in itself the tumor forming agency, and whatever a tissue can produce out of its own cellular structure, if it can be proven that the tumor producing agency is not a bacterium, must be a product of the cells themselves, and very probably inherent in the cells.

COMPARISONS OF THE RELATIVE OSMOTIC PRESSURES OF NORMAL CELLS AND CARCINOMA CELLS OF THE SAME ORGAN. Normal cells,

as well as carcinoma cells, can be isolated from their stroma by pencilling portions of fresh tissue in salt solution, isotonic with the blood plasma. The strength of this solution will vary with different animals. The serum of human beings is, according to H. J. Hamburger,<sup>1</sup> isotonic with a 0.84 to 0.89 per cent. solution of sodium chloride. I have observed cells from a carcinoma of the stomach in such salt solution on the warm stage, and compared them with the cells of normal stomach tissue. Whilst there was no apparent change in the normal gastric cells the gastric carcinoma began to contract in the course of the day, four to five hours, as if they were in an hyperisotonic solution. Not all cells of gastric carcinoma that are pencilled out in an isotonic salt solution will show this contraction. One notices that in perhaps one-fourth to one-third of the cells there is no contraction evident. I have gained the impression that although carcinoma cells represent cells that are emancipated from the laws of normal proliferation (if I may speak of such laws), nevertheless the carcinoma cells themselves, although alienated from the general cell state, may be healthy or diseased. By healthy in this sense I do not mean that they are normal cells; but simply that they represent a condition of the cells as occurs in the majority of cancers before they begin to disintegrate. When a cancerous tumor undergoes necrobiosis certain of its cells undergo a still further pathological process and it is in these cancers undergoing cellular destruction in which the perfect lawlessness of the cancer cell becomes manifest. I am of the opinion that those cancer cells which do not act like the majority in isotonic salt solution are perhaps already undergoing the beginning changes of necrobiosis. The majority of cancer cells show a contraction, whereas this minority does not show this phenomenon. Difference in staining of the protoplasm and chromosomes can also be observed in these two kinds of cancer cells. I am in doubt whether this phenomenon of contraction or swelling, as the case may be, would be possible in the cells of all types of cancer. The adenocarcinoma of the stomach is derived from an epithelial and glandular cell which even normally gives evidence of marked regenerative power. It possesses marked mutability, as Virchow would say, and these powers are still manifest when this cell becomes emancipated from the normal laws of proliferation. I have not been able to try the experiment, but I doubt whether the cells of an osteoma, chondroma, or scirrhous would be capable of undergoing visible osmotic changes under the microscope, no matter how different the osmotic tension of their environments would be made from the tension existing within their protoplasm.

Similar observations were made with the cells of a mammary carcinoma, comparing their behavior to that observed on normal mammary

<sup>1</sup> Osmotischer Druck und Ionenlehre, p. 445.

gland cells in isotonic solution. I have also compared the behavior of normal gastric gland cells with those of a gastric adenocarcinoma after they had been pencilled out in the blood plasma of the same patient, and also in the blood plasma of another but normal individual. The same differences were found between the two in blood plasma as observed in isotonic salt solution. These studies led me to suspect that a deep-seated disturbance exists between the osmotic tension of the living cells of a cancer and the surrounding juices, mainly because the cancer cells act differently from the normal cells of the same tissue when placed in the same isotonic solution or in blood plasma of the same individual. Thus far these studies have been made only in mammary and gastric adenocarcinoma, and I would caution against the extension of the observations to all forms of tumors until these have been thoroughly studied in this way. It must be emphasized here that as these pieces of tissue could only be gained at operation, I was restricted in my search for normal cells to tissue in the immediate neighborhood of the malignant growth. It is probable that cells of the same organ, more remote from the malignant growth, might have shown a still greater contrast. I am now studying the behavior of normal cells observed in cancer juice expressed from a cancer of the same organ. Normal cells of an organ observed in such cancer juice will give evidence of swelling in the course of three to five hours. These phenomena might be interpreted by differences in osmotic tension between the protoplasm of the cell and the surrounding solution. For instance, if a normal cell swells up in filtered cancer juice, we may be correct in assuming that it takes up water, that the cancer juice contains relatively more water than the protoplasm of the cell. Increase of volume of the cell, if associated with cytolysis, may be due, however, to the presence of toxic substance in the cancer juice. This has at present not yet been satisfactorily investigated. The fact that the majority of healthy cancer cells contract in salt solution isotonic with blood plasma would indicate that they have lost water. It is justifiable to assume that the osmotic tension between a cancer cell and the normal cancer juice as existing in its environment is isotonic, for a cancer cell will not change its volume in cancer juice. However, in the production of this juice it is unavoidable that the cancer cells are cut and bruised and considerable of the cytoplasm of the cancer cell may be contained in it, which is not present in the juice bathing the cancer cells in the ordinary state of these growths. Material is very difficult to obtain, for although the cancer tissue is readily obtained from operators, they do not, as a rule, cut far away from the limit of the growth into the normal tissue in an effort to remove it.

These are purely physical conditions, but they show a definite disturbance of osmotic tension.



Phenomena of cell division are as Bütschli, Quincke, and Jacques Loeb believe, phenomena of protoplasmic streaming. They require, as Quincke has shown, a definite degree of viscosity. We have to remember that all life phenomena, normal as well as abnormal, are ultimately due to motion, or changes occurring in colloidal matter.<sup>1</sup> No protoplasmic motion can occur if the normal viscosity of this matter is disturbed in either direction, that is, if it is too great or too small. It may be that the disturbances in osmotic pressure, which I have suggested in the preceding, may lead to changes in the viscosity of cell protoplasm, either favoring or inhibiting cell division.

CHANGES IN VOLUME WHICH NORMAL CELLS UNDERGO IN CANCER JUICE. Studies on osmotic pressure made by means of the hematokrit, according to the methods of Hedin<sup>2</sup> and Köppe,<sup>3</sup> indicate that normal cells of the stomach or mammary gland cells when placed in cancer juice derived from a gastric or mammary cancer, swell up as if they were in a hypisotonic solution. The red blood cells of normal human beings and also of cancer patients will lose some of their coloring matter when placed in sterile cancer juice or sterile filtrate made as described in the preceding portion of this article. This would, in some of my studies, occur even when this filtrate or cancer juice was made isotonic with the blood plasma, and is suggestive of a substance in the cancer juice which is capable of making the stroma of the blood corpuscles permeable to toxic or other substances capable of effecting dissolution of the hæmoglobin; and reminds one of the experiments of Belfante and Carbon,<sup>4</sup> and also those of J. Bordet.<sup>5</sup> These experiments demonstrated that toxic substances are formed in the blood serum of animals into whom blood of another animal species had been injected. If the blood of a rabbit is injected into the peritoneal cavity of a guinea-pig, the serum of the guinea-pig blood will acquire the property of destroying the red blood corpuscles of rabbits, a property which the serum of normal guinea-pigs does not possess. If 5 c.c. of serum of a normal guinea-pig are injected into the circulation of a rabbit, this animal is in no way influenced thereby. But if this serum is derived from a guinea-pig which has previously received several injections of rabbit blood, then it becomes dangerous to a rabbit. A few minutes after the injection the rabbit dies and the autopsy reveals extensive dissolution of the blood and numerous hemorrhages as a consequence. Similarly the blood of the guinea-pig can be made to acquire a destructive property upon cholera bacteria after a small amount of a culture of cholera vibrios have been injected into the peritoneal cavity of the guinea-pig. Ehrlich

<sup>1</sup> Jacques Loeb, "The Comparative Physiology of the Brain, etc., p. 14.

<sup>2</sup> Skandinavisches Archiv. f. Physiologie, 2, 134, u. 360.

<sup>3</sup> Dubois-Raymond's Archiv., Physiol. Abt., 1894, 154.

<sup>4</sup> Referred to by Metschnikoff, Annals of the Institut Pasteur, June, 1900, No. 6, p. 370.

<sup>5</sup> Ibid., October, 1898, April, 1899.

and Morgenroth<sup>1</sup> and the other authors agree that this hæmolytic and bacteriolytic action of guinea-pig serum is due to two substances, one of which they speak of as a "sensibilisator," and the other as an "alexin." It is the penetration of the "alexin" into the red blood corpuscles which makes it lose its coloring matter, but this "alexin" cannot work unless the blood corpuscles have been sensibilized by the other agent. The "sensibilisator" is formed in the circulation of the guinea pig by the intraperitoneal injection of rabbit blood. The "alexins" are normally present in the circulation of the animal. It was discovered that the sensibilizing substance can tolerate a temperature of 70° C. without destruction, but that the "alexin" is destroyed at a temperature of only 55°. I have said that the normal serum of the guinea-pig contains "alexins," which are preserved, of course, in the serum made active against the blood corpuscles of the rabbit. If the active guinea-pig serum is heated to 55° the "alexin" is destroyed, but the sensibilizing substance remains active. In such a serum the rabbit blood corpuscles retain their coloring matter, for the "sensibilisator" is not capable of producing hæmolysis. But as soon as serum from a normal guinea-pig or a normal rabbit is added, the coloring matter of the blood corpuscles begins to part from the red blood cells, for both the normal guinea-pig as well as rabbit serum contain "alexin." These agents which produce hæmolysis partake of the nature of catalytic agents. Ehrlich and Morgenroth speak of "*Zwischenkörper*" (intermediate bodies), and also of "*complement*." In none of these investigations is it stated that these substances have been isolated.<sup>2</sup> The speculations concerning them are based exclusively upon an observation of their effects. They were important for me, however, in suggesting the idea that perhaps the cell growth representing cancer might in some way be associated with the influence of a catalytic agent which could be studied in a similar manner by its effects on the normal cells of the same tissue or upon the blood cells of the same or normal individuals. The effects which I have observed of cancer juice on normal cells of the same organ, and of cancer juice and cancer filtrate upon blood corpuscles, throw no direct light upon the pathogenesis of malignant growths. They were undertaken merely because such studies had, to my knowledge, not been undertaken heretofore, and I felt that I was following the injunctions of Julius Robert Mayer that a phenomenon should be studied from every possible aspect before we should seek consolation in an hypothesis. Then again there was the hope that some reaction might be discovered whereby we might be enabled to tell what was a malignant growth and what was not, by the effects of the juices of a

<sup>1</sup> Berliner klin. Wochenschr, 1899, Nos. 1 and 22.

<sup>2</sup> I shall apply the inspiration gained from the work of Bordet, Ehrlich, etc., in the explanation of the rarity of metastases, under the heading of "Metastases," later on.

malignant growth upon normal cells. This has, so far as my work is concerned, not as yet been successful. The question is so manifold and the liability to error in whatever direction one goes is so great, that no practical conclusions should as yet be drawn. A weak point of these investigations consists in the fact that the juices and filtrate extracts of benign growths have not as yet been studied in their possible action upon cells of the same organ, or upon blood cells, nor even have the tissues and filtrate extract of normal tissues in their actions upon each other been studied satisfactorily. The question might be asked, "Does the tissue of an entirely normal stomach contain an agent concerned in the cell growth of gastric tissue which on being extracted from a whole stomach, concentrated by aseptic evaporation, and injected into normal gastric tissue of another animal of the same species, will cause increased growth of that tissue?" For the development of the growth of the mucosa we would have to limit ourselves entirely to extracts of the mucous membrane, for the stomach contains layers of widely different cellular structure. If such an extract of mucosa does not affect the normal stomach would it cause cell proliferation after being injected into the edges of a gastric ulcer? As the difficulties of this investigation seem almost insurmountable, depending largely on procuring proper and abundant material, I have given expression to these suggestions with the hope that they may be of value to other investigators.

This much I will have to emphasize, "Whatever the substance or agent may be which causes a benign canine gastric ulcer to be transformed into an adenoma," it is destroyed when the filtrate is heated to 60° C. (140° F.); for while four animals out of ten injected with the unheated filtrate developed adenoma, no such result followed in six animals afflicted with gastric ulcers when they were injected with the filtrate that had been heated to 60° C.<sup>1</sup>

PROBLEMS OF CELL GROWTH. All of these questions are intimately related with the *problems of cell growth*. The immediate and specific causes of cell division are still imperfectly known. Is cell proliferation due, as Ribbert<sup>2</sup> thinks, exclusively to the removal of inhibition or restrictions to growth in the environment of the cell, or is it due to proliferative forces within the cell? We have thus two conceptions of the immediate causes of cell growth, one without and the other within the cell. According to Thiersch and Boll, each tissue continues to grow up to the limit afforded by the resistance of neighboring tissues or organs. In the fully developed body the mutual relations of the cells are of such a nature that the conditions for further proliferation are unfavorable. Ribbert and others express

<sup>1</sup> I am refraining from designating the proliferation as carcinoma for reasons given at end of article.

<sup>2</sup> Loc. cit., p. 300.



this in the term "tissue tension" ("*Gewebe spannung*"), which prevents an increase of growth in the cells. They understand by this "tissue tension" all the mutual influences of the tissue constituents upon each other; they do not exactly mean mechanical pressure, although this no doubt plays an important rôle in restricting growth. The removal or lessening of this resistance to growth through injury or disease causes the resumption of growth and cell division, leading either to regeneration of lost parts or the formation of abnormal growth. According to the precedent of Virchow, it was formerly held that not only the function of a cell, but also its growth could be directly caused by the action of external stimuli. Virchow distinguished, accordingly, between functional, nutritive, and formative stimulation. This doctrine was contested by Weigert, whose efforts to disprove the power of external agencies to stimulate directly cells to proliferation have been very instructive. Weigert postulates that some primary injury to the tissues, as the immediate effect of chemical, mechanical, and other external agencies, is necessary to stimulate growth. This postulate has been fulfilled in many instances where such a cell injury had not been previously suspected. Better methods of investigation will no doubt enable us to demonstrate such an injury to the tissues. At the same time it is going too far, in my opinion, to attribute all morbid cell growth to such cell injury. In a comprehensive way Weigert's theory may be stated as follows: Cells are incited to growth through removal of obstacles to growth in the environment, in consequence of some disturbance in the normal relations or equilibrium of the cells with surrounding parts. The capacity of cells to proliferate has become latent when a certain "tissue tension" has been reached; it has become potential by the establishment of definite relations between cells themselves and between the cells and the basement substances, bloodvessels, lymphatics, tissue juices, and chemical substances contained in them.

We have hitherto studied cell growth as conceived to be due to a removal of restriction to proliferation outside of the cell body. In all these cases, however, it is difficult to determine the immediate stimulus to cell division, for a long chain of causes and effects may intervene between the primary disturbance and the ultimate reaction of the dividing cells. The opinion is gaining ground that the immediate causes of cell proliferation, whatever their antecedents, are to be sought in local chemical changes. Recent experiments on the proliferation in the ova of various invertebrates, conducted by Jacques Loeb, T. H. Morgan, R. Hertwig, and Mead, give ground for the conclusion that the stimulus to cell growth is of a chemical nature.<sup>1</sup> The climax of these experiments is reached in Loeb's artificial production of parthenogenesis in sea-urchin

<sup>1</sup> Edmond B. Wilson, "The Cell in Development and Inheritance," second edition, p. 391.

eggs by treatment with dilute magnesium chloride. The remarkable gall formation in plants leaves no doubt that extremely complex abnormal growths may result from specific chemical stimuli, and pathologists have held that abnormal growth in the animal body may also be incited by abnormal local chemical conditions. Only in two ways, then, can the cell be incited to growth—either by the removal of resistance to growth in the environment or by an increase in the formative energy resident within the cell. William H. Welch<sup>1</sup> concedes both of these possibilities—*i. e.*, forms of energy acting from without directly increasing the formative energy of the cell, and stimulating it to growth and multiplication; and, secondly, increase of the proliferative forces naturally latent (dormant) within the cell. It will be difficult to decide in which of the two ways cell proliferation is brought about. One reason for assuming that in carcinoma of the stomach the tumor producing agency is to be sought in increase of the proliferative forces within the cell is the fact that these cells must be ground up and crushed very thoroughly before the extract will have any cancer converting effect upon experimental gastric ulcer. If the tumor producing agency were some chemical substance in the environment of the cell, we should not expect that thorough crushing and grinding were necessary to extract it, but that it could be dissolved out by repeated percolation and irrigation. However, this is an unreliable test, as the tissues must be torn up into small pieces in both instances, even if only to permit percolation. The fact that it is possible to extract a tumor producing agency from gastric carcinoma by crushing pieces of it in normal salt solution would not permit us to decide whether the tumor producing substance was derived from within or without the cell.

The modern view that cancer metastases can be effected by the transportation of single carcinoma cells is a support of the contention that the tumor producing agency is resident within the structure of the cell.

In a recent investigation on the fate of dislodged and embolized tissue particles in the animal body, Paul Lenger mann comes to the conclusion that the power of producing metastases is dependent upon an increase in the proliferative energies inherent in the cell, and not upon a reduction of normal tissue resistance to growth.<sup>2</sup>

Speaking of the influence of cell nutrition and the maintenance and undisturbed progress of cell function, Ludolf Krehl<sup>3</sup> says: "Nobody will expect that a tissue can maintain form and size without sufficient supply

<sup>1</sup> Adaptation in Pathological Processes, THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, June, 1897.

<sup>2</sup> "Schicksale verlagter u. embolisierter Gewebsteile im thierischen Körper," p. 69, in "Arbeiten a. d. Pathol.-Anat. Abtheilung d. kgl. Hyg. Institut." Posen, 1901, s. 299, O. Lubarsch.

<sup>3</sup> Patholog. Physiologie, second edition, p. 532.

of potential energy ; but the incentive does not come from the blood, as was formerly believed, but always from the parenchyma itself."<sup>1</sup>

INFLUENCE OF PHYSICAL LAWS ON CELL GROWTH. Oscar Hertwig investigated the influence of temperature on the recently fertilized ova of *rana fusca* and *rana esculenta*, and found that certain well-recognizable stages ("Stadien") in the development of these eggs were reached quicker as the temperature of the breeding medium was increased.<sup>2</sup> He found that the same relation existed between rate of growth and temperature as was known to exist between reaction time and temperature.

Cell volume, within certain limits, is dependent upon osmotic pressure. Cells can be made to undergo apparent growth by placing them in solutions the osmotic pressure of which is below the pressure within the cell protoplasm. In this case the cell volume increases by the diffusion of water into the protoplasm. Loeb<sup>3</sup> cut off the polypi from colonies of *tubularia*, and brought the stems in sea water of various concentrations and dilutions. He found that polypi again grew out of the stumps as long as the sea water was not concentrated to more than 70 per cent. of its volume or not diluted more than to 225 per cent. of its original volume with water ; but the regeneration occurred prompter and quicker in the diluted than in the concentrated sea water. Loeb's experiments show conclusively that moderate dilution of the external medium in which a cell is bathed favors growth—*i. e.*, the solution outside must be a hypotonic one. Two other essential physical conditions to growth are (1) a certain turgescence (turgor) within the cell, and (2) expansibility of the enclosing protoplasmic envelope.

It is conceivable that cell protoplasm will become more expansible and looser by the reception of water from the hypotonic environment and a certain turgescence—that is, a hypertonic state within the cell metabolism, and the consequent increase of osmotic energy connected therewith. Increase of turgidity is always seen in rapidly growing parts. Turgidity means osmotic entrance of water into the growing cell. Claude Bernard<sup>4</sup> found that blood flowing through a secreting gland had lost water, and Ranke found that blood that had streamed through a working muscle had lost water.<sup>5</sup> To complete the logic of these instructive observations, Loeb demonstrated that the water thus lost was taken up into the substance of the working muscle ; for when the muscle while at rest and before work was placed in a solution which was isotonic with the protoplasmic contents of the muscle cell, it increased in weight during its work<sup>6</sup>—that is, the augmentation of

<sup>1</sup> "Nicht von aussen zugeführte Kräfte bringen das Heil, sondern die Zelleschaft es sich selbst."

<sup>2</sup> Archiv. f. mik. Anat. u. Entwicklungsgesch., 1898, 52, 319.

<sup>3</sup> Organbildung und Wachstum, Würzburg, 1892.

<sup>4</sup> Phénomènes de la vie, 2d edit., i., 169.

<sup>5</sup> Tetanus Physiologie, 1868, 89.

<sup>6</sup> Pflüger's Archiv., Bd. lxxi., 439.



metabolism during work had evidently increased the osmotic pressure within the muscle cell, and the ensuing difference in pressure had induced the growth.

These observations are important for the interpretation of my own studies demonstrating the contraction of fresh cancer cells in solutions made isotonic with the human plasma, or in blood plasma itself, as if they were in a hypertonic solution—a phenomenon not observed when normal cells of the same tissue from which the cancer was taken are placed in the identical plasma or solution. It will hardly be necessary for me to emphasize that any and every growth of and in cancer cells cannot be attributed to the taking in of water only, nor can a muscle hypertrophy due to work be attributed to the taking in of water exclusively. The water osmosis is only one phase of the process of growth, that phase which by effecting an increase of volume impresses us most as growth. The internal construction of the cell household, the deposition of new cytoplasm, is concealed from us.

When frog larvæ are analyzed at different stages of development for their percentage content of water and solid substance it is found that the entire growth of the first fourteen days consists in the incorporation of water. The body weight becomes ten times as great by water, and not until after this does the interior construction and the deposit of solid substances into the aqueous tissue begin. In the first two weeks of development of batrachian larvæ the percentage of water in the embryo rises from 56 per cent. to 96 per cent.,<sup>1</sup> thereafter it begins to sink again.

In the light of our present knowledge we have a right to speak of the "osmotic pressure of the cell," for the cell protoplasm, as previously emphasized, is a liquid, a solution, or at least in a state of viscosity. The entrance of water into the cell substance is brought about primarily by metabolic changes effecting a hyperisotonic state in the cell with regard to its surrounding liquid environment. *This phenomenon of change of dimensions (contraction) of fresh carcinoma cells (gastric adenocarcinoma in normal plasma or solutions isotonic with plasma) is to me strong evidence in favor of the view that whatever other causes for the excessive growth of malignant cells there may be, certainly some of the causes are resident within the cell protoplasm itself.*

When we approach a consideration of the question of how the cell builds up protoplasm—that is, an inquiry into the methods and means by which it carries on the synthesis of its substance—we are confronted with a problem apparently presenting insurmountable difficulties, for all artificial syntheses are brought about by forces and agents which can never be conceived as participating in the processes of life. Such agents and forces are high pressure and temperature, concentrated

<sup>1</sup> Davenport. "Rôle of Water in Growth," Proceedings of the Boston Society, 28, 73, 1897

inorganic acids, free chlorine, and galvanic currents of high tension. All of these are factors which would destroy cell life instantly.

So far we know definitely of the synthesis of albumin is only by the aid of enzymes (catalysator). For instance, the reconversion of albumoses, which have been formed in the gastro-intestinal canal into albumin, is attributed to some agent in the gastric wall.<sup>1</sup> When the stomach is isolated from an animal, but kept alive, at the height of digestion all albumoses disappear from it. It might be presumed that this does not indicate a synthesis, but a further breaking down of the albumoses. In that case, however, an increase in the non-precipitable nitrogenous substance should be demonstrable, which is not the case;<sup>2</sup> so that any other interpretation of this disappearance of albumoses, except their synthetic reconversion into albumin, appears illogical. Furthermore, Danilewsky and Sawgaloff have proven that chymosin (rennin) is capable of synthetically constructing an albumin from peptones and albumoses in an acid medium. This albuminous body, which they designated as "plastein," is soluble in weak acids and alkalis, insoluble in water, and can be precipitated by strong salt solution—undeniably a typical albumin constructed synthetically by this ferment.

It would be going too far to assume that all syntheses in the organism are enzyme syntheses, for an enzyme (catalyzer) is *incapable of producing anything that would not also be produced without it by other means*. Ostwald<sup>3</sup> groups all ferment or enzyme actions under the term "catalyse," by which he means *the acceleration of a slow or the retardation of a rapid chemical process through the presence of a foreign body (catalysator)*.<sup>4</sup>

This definition gives the specific characteristic of enzyme action. An enzyme can, therefore, not carry out a process which would be impossible without it, but it can only influence the time in which a chemical process occurs, generally increasing the rate of the reaction, which would also take place, in a much slower or faster manner as the case may be, however, without it.

The facts, namely (1) that albumin can be constructed synthetically by enzymes, and (2) that enzymes act merely as accelerators or inhibitors of processes that can occur without them, coupled with the experimental results briefly narrated in the preceding (acceleration of cell proliferation by injection of a cell-free and sterile fluid), should suggest the possibility that abnormally rapid formation of protoplasm such as is observed *in the marvellous cell-proliferation of malignant tumors may in some way be associated with the action of an enzyme*. The catalytic origin of malignant neoplasms is by no means proven by these facts and

<sup>1</sup> Hofmeister. Zeitschr. f. Physiol. Chemie, 6, 69.

<sup>2</sup> Glässner. Beitr. z. Physiol. u. Pathol. Chemie, 1902, i., 328.

<sup>3</sup> Loc. cit.

<sup>4</sup> See W. Ostwald Ueber Katalyse, Leipzig, 1902.

considerations, but only made more probable. I have previously emphasized the important rôle which physical processes (osmosis) play in the growth of cells, so that it is not logical to attribute proliferation to enzyme action alone; but as we have seen that even this osmosis is due in part to a preceding hyperisotonic state within the cell brought about by increased metabolism, the function of a catalyzer is even here not inconceivable, but on the contrary very probable. Much remains to be proven before we are justified in making this conclusion indisputable.

Thus far attempts to isolate enzymes have failed, for what are believed to be ferments are variously considered, albuminous or proteid bodies — albumoses or peptones (Uróblewski) — or nucleoproteids (Pekelharing's conception of pepsin), in connection with which ferment actions have been observed. In brief, nothing is definitely known of the chemical nature of organic enzymes.

When it comes to the problem of isolating enzymes from protoplasm of cells we find that it presents insurmountable difficulties. It might be thought that inasmuch as enzymes are chemical substances, some of which are known to exert their characteristic action apart from the living substances to which they are usually attached, it might be possible to destroy the cell alone and extract the enzyme; but all protoplasmic poisons are also enzyme poisons (corrosive sublimate, carbon monoxide, sulphuretted hydrogen, hydrocyanic acid, nitrate of silver, formaldehyde, hydrogen peroxide). J. R. Green has emphasized that protoplasm itself has powerful fermentative activity. No matter what the exact relation is that the intracellular enzyme has to the protoplasm, whether it be conceived to be a detached protoplasm molecule or not, as long as it is considered a derivative of protoplasm it must be self-evident that protoplasm is capable of doing all those things which the enzymes can do. Newer conceptions concerning this subject attribute to protoplasm much more wonderful achievements than to the enzymes themselves. If the efforts to separate growth stimulating enzymes from cell protoplasm are at present futile, from the insurmountable chemical difficulties involved, we should realize that protoplasm itself may exert a more intense catalytic action than any enzyme derived from it. Our reflections concerning the nature of a substance which we assume to be capable of stimulating cell growth, and which is cell free and sterile, must end here for the present. We can only say that the agency is contained within the cell, but whether it be a special derivative of the cell protoplasm or the protoplasm itself, it is, in the light of our present knowledge, impossible to decide. A slight hope of advance lies in researches showing differences in the degree of temperature which the protoplasm and the ferment can stand without destruction. I have gained the impression that some ferments are much more susceptible to



high temperatures than the protoplasms from which they are derived. For instance, the gastric mucosa of a dog can be heated to a temperature of 158° F. (70° C.) without absolutely destroying the tissue; but heating pepsin to this temperature for three hours will destroy its activity permanently. Similarly, when the so-called "commercial" pepsin is heated to a temperature of 55° to 60° C. in a moist condition it is destroyed (in a thoroughly dry state it may tolerate 160° for a short time). Nevertheless the chemical composition of the nucleo-albumin is still there as it was before the heating. The fermentative power has disappeared. Evidently ferments are not nucleo-albumins in the ordinary sense of the chemist, but something attached and associated with these nucleo-albumins.

CONCERNING THE STRUCTURE OF PROTOPLASM AND ITS CHEMICAL ORGANIZATION. The method that has become most common to familiarize us with the structure of living substance has been to start from histological elements visible under the microscope and to attribute certain physiological functions to them. The conceptions thus derived have not always acquired precision, and we have definite notions only concerning the coarser elements visible under the microscope, such as the nucleus, the chromosomes, etc. This method of observation has not been able to give the least explanation of the finer elements of the cells, the innumerable droplets, barely visible vacuoles and granules of the protoplasm, not to speak of that still finer subdivision of cell protoplasm which might be designated as ultra-microscopic. It is very gratifying, therefore, that biochemists have approached the subject of the construction of the living substance from the purely chemical standpoint, as, for instance, Franz Hofmeister has done (*Chemische Organization der Zelle*), who did not start from the visible architecture of the cell or protoplasm, but from its achievements and functions. He tried to investigate how protoplasm must be constructed in order to make these functions possible. As the functions of protoplasm are above all things chemical, he entered exclusively upon chemical considerations.

The hepatic cell furnishes us with an instructive example of how many chemical processes may go on in one and the same cell, and very probably go on simultaneously. We know definitely that the liver cell forms glycogen from sugar, and, reversely, sugar from glycogen. It forms urea from ammonia and amido acids. It decomposes hæmoglobin, and under the splitting off of iron it converts it into bilirubin. It can manufacture cholic acid from a substance still unknown, and pairs it with taurin and glycocholl. This same cell can combine phenols with sulphuric acid to form the ethereal sulphates, and it can retain or render harmless poisons that are conducted to it. Nothing is more certain than that these performances represent only a fraction of the chemical

versatility of the hepatic cell, for we must certainly assume that the same cell can in addition execute other chemical processes necessary for the oxidation of the food materials brought to it for hydration and assimilation. The supposition that there is a division of labor among the liver cells, one group of cells manufacturing one product and the other another, is untenable because the hepatic cells are of the identical structure throughout the liver, and their relation to the blood, lymph, and biliary vessels so alike that an assumption of a division of labor is not justifiable. There is no escape from the conclusion that all liver cells are chemically equivalent, and each cell is capable of performing all of the described chemical processes and possibly many more. When we reflect that all this chemical activity is invisible by the microscope, and that many chemical processes must occur side by side simultaneously, it is difficult to conceive of the construction of protoplasm that would make such a manifold and wonderful chemical activity possible.

Many years ago Hoppe-Seyler expressed the opinion that such activities in living cells as were intelligible at his period were due to enzymes, and since then it has been possible in many cases to extract such intracellular ferments from the innermost structure of the cells and to establish their significance for vital processes. When we compare the instrumentarium—chemical substances and reagents necessary for chemical transformations in the laboratory—with the processes as they occur in living protoplasm (as much as has thus far been accurately observed) we cannot fail to be impressed with the astounding simplicity and conformity to the end in view exhibited in the means which protoplasm employs to accomplish its chemical purposes. In order to induce a reaction in the laboratory we need a reagent, *i. e.*, either an alkali or an acid, or perhaps the application of heat; but the reagents which the cell employs are calculated to fill the chemist with envy.

The food substances and the oxygen and other possible stuffs which act upon each other within the cell do not, as a rule, belong to the normal cell household, but enter it from the blood. The reagents, however, which induce the reactions, must always be present, and they must in some way be protected from being washed out of their domicile by the constant flow of liquid passing through the cell. These reagents must be either soluble in water or infinitesimally divided in it. They must be capable of accomplishing relatively large chemical performances, and not be consumed or used up during their activity. Such qualities are only known to be possessed by agents which the chemist has designated as *catalyzers*. The bearers of the chemical energy in the cell are catalyzers of a colloidal consistency (Hofmeister). According to Hofmeister, we are justified in assuming that the living cell protoplasm contains all the ferments necessary to the execution of the chemical performances observed in connection with that cell.

This view is supported by the knowledge obtained of the physiological chemistry of quite a number of cells in the animal body. For instance, we know that the hepatic cell can yield up (1) a proteolytic ferment, (2) a ferment that can transform combined nitrogen of amido acid into ammonia, (3) a fibrin ferment, (4) a glykase, (5) a maltase, (6) a ferment capable of splitting up nucleins, (7) a lactase, (8) an aldehydase, (9) a lipase, and (10) a ferment similar to the gastric chymosin. Here we have definitely established the presence of ten different ferments in a single hepatic cell. *In addition to this we may believe that the synthetic construction of the cell tissue itself requires a special ferment to make possible the chemical processes necessary for the upbuilding of protoplasm.* From what I have said in connection with normal and abnormal cell growth *it is evident that it is this ferment to which must be ascribed the power of accelerating or inhibiting cell growth.* If we once accept ten different ferments which really have already been definitely established as existing in the same cell, there is no logical reason why the remaining unexplained chemical functions of the cell should not also be ascribed to peculiar ferments, and *I can conceive of no reason why cell growth itself should not be accelerated or inhibited, as the case may be, by a particular enzyme.*

A considerable number of capable modern physiologists have accepted the view that every chemical reaction in the cell has its particular catalyzer corresponding to it. It is easy to recognize that this view may lead us too far, for the specific nature of the ferments is not always such as to restrict their action on one single chemical body, but they may be able to transform a greater or lesser number of substances of similar construction (tyrosinase, for example, may oxidize a large number of aromatic substances). Furthermore, it is conceivable that very labile bodies may arise as a result of chemical transformations in the cells, which are promptly changed into other forms under the existing conditions, and, therefore, no ferment is necessary to explain such transformation. A further revelation which modern chemistry has brought particularly through the researches of Kastle and Loevenhart, to which I have already referred, is the reversibility of the action of ferments. Should this power of reversibility of enzyme action be confirmed with other ferments, it opens up the possibility that many analyses and syntheses are brought about by the same ferment according to the existing requirements and chemical conditions in the cell.

It is probable that the chemical organization of the cell is capable of reckoning with all possibilities, whether they occur within or without the cell, whether they are an advantage or hostile to the cell state. There are no reliable reasons for believing that the organic antitoxins, coagulins, and antihæmolysins owe their origin to definite catalytic cell agents which are equipped for the production of such protective sub-



stances. M. Jacoby holds that the antibodies do not act like ferments. The cell is even equipped with ferments for the purpose of committing suicide or digesting itself when it has arrived at a state or condition in which it is no longer of use to the cell state. This phenomenon of cellular autodigestion has recently been observed in tissues which have been perfectly protected from the invasion of micro-organisms.

*Cellular autodigestion* has been studied in all animal organs and occurs in all except those that show a very slight degree of metabolism. M. Jacoby gives to this phenomenon the designation autolysis. It is well known that the various forms of lymphoid cells contain an abundance of a trypsinoid ferment, and it is possible that autodigestion occurs by virtue of such an enzyme. Petrey<sup>1</sup> found that in neoplasms autolysis was much more intense than in normal corresponding tissue. The proteid substances and the nucleins of the cell, the glycogen and the fat, are split up similarly as they would be in the intestines, and a number of diffusible substances result, such as sugar, leucin, tyrosin, fatty acids, etc. This is a form of catalytic colliquidation occurring in single cells, or in cell complexes which have passed the stage of their usefulness; and if this process occurs in an otherwise normal organism there is no reason why the end-products of such cellular autodigestion should not be taken up by the blood and lymph and be absorbed and assimilated to the advantage of the general organism just as they would be if they had been absorbed from the digestive tract.

An astounding fact which has been revealed by modern investigation in connection with this phenomenon is that bactericidal substances are set free during autolysis. It is well known that proteolytic digesting mixtures are first-class culture media for bacteria. For this reason the production of bactericidal substances during cellular autodigestion demands admiration.

If I have in the preceding suggested the probability of the action of intracellular catalytic agents in accelerating or inhibiting cell growth, I do not wish to be understood as meaning that these agents are the only factors which determine the growth and the character of the cell protoplasm. What I have said concerning the rôle of osmosis will prevent my being misunderstood in this connection. An intracellular enzyme cannot construct protoplasm out of itself—it can only build it up out of the materials furnished to it; and as these materials must vary with every species and even with every individual, it is probable that the elements of which protoplasm is constructed within the cell must be presented in a certain definite form, in order that a normal cell protoblast shall result. This is an important point, for it

<sup>1</sup> Hofmeister's Beitr. z. chem. Phys. u. Path., 1902, ii.

explains how variations in the chemical composition of the cell juices (dyscrasias) may be determining factors for the character of the resulting cell structure.

The simultaneous action of so many intracellular ferments within the same cell sometimes representing diagonally opposite processes, such as oxidation and reduction, hydration and the withdrawal of water, is only conceivable if we accept, with Professor Edmund B. Wilson, the foam structure of protoplasm, that is the view which assumes that protoplasm is held within a foam-like structure of countless ultra-microscopic compartments, retorts, or vacuoles. We must assume also that the walls of these ultra-microscopic spaces are not affected by the reaction which takes place within them. For instance, that the walls of the compartment or vacuole in which oxidation takes place are resistant to the oxidase, and that the walls of the space in which proteolysis takes place are resistant to the proteolytic enzyme. Such a possibility is, so far as our present knowledge goes, only conceivable within the living cell by means of its catalytic agents, which may decompose an albuminoid body of one composition completely and yet leave another very similar albuminoid body entirely intact. For instance, the proteolytic ferment of the liver can completely decompose the globulin of the hepatic substance, but it does not attack another albuminous body of similar composition with which it may even be in contact. The intactness of this so-called foam structure of protoplasm is, therefore, an essential condition for the normal action of the intracellular enzyme. A destruction of these ultra-microscopic partitions may lead to serious consequences, and it is here that the importance of what Welch calls the "more subtle and partial damage of cytoplasm and nucleus" exercises its detrimental influence in destroying the normal intracellular architecture and making possible the liberation of ferments and disturbing the normal chemical equilibrium.

We must conceive of the normal and orderly performance of the cell as brought about by the aid of an admirable and highly sensitive system, embracing among other things a transference and transformation of chemical, electrical (ions) and other specific forms of energy, and of accelerating and inhibiting enzymatic (catalytic) agents; of the latter a great variety, each acting in its own ultra-microscopic compartment. We must conceive of a delicate mutual adjustment and conformation to purpose among the many little laboratories within the cell household. And even these conceptions are coarse and inadequate if we knew in reality of the incomprehensible fineness and perfection of intracellular chemical activity. But it will be readily understood that very slight damage to cytoplasm in the sense of Welch<sup>1</sup> will be sufficient to destroy

<sup>1</sup> THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, JUNE, 1879, p. 19.



this beautiful arrangement, and enzymes which are useful lambs in the orderly household may become destructive lions when the partitions are broken down.

In the preceding I hope to have made possible the conception that abnormal cell growth may be due to something else than bacteria. At the same time I do not wish to deny the possibility of a deleterious influence exerted by bacteria and favoring the development of malignant neoplasms. Malignant neoplasms represent a great group of abnormalities, and I agree with Hanseemann that there cannot be a uniform cause for all these manifold types of abnormal cell growth. But if I admit the possibility of bacteria as active in their etiology, it is only as indirect agents in causing these more subtle and partial damages, to cytoplasm, which liberate ferments on the one hand, and destroy them on the other; for we must not lose sight of the possibility that even within the cell abnormal growth may be due to excessive action of one ferment stimulating growth, or to the absence of an enzyme necessary to inhibit it.

REVERSIBILITY OF ENZYMES. Basing our views on the chemical mechanism of growth on the phenomenon of the reversibility of enzymes, it is intelligible how increase in the dimensions and weight of the cell mass may be brought about by two different and divergent processes. There may be only the synthetic enzyme concerned in the control of growth, or there may be a second intracellular enzyme that inhibits growth, by analysis of protoplasm already formed. Under the conception of enzyme reversibility, however, it is not necessary to assume the existence of two distinct enzymes—one synthetic, the other analytic—for reversibility means that one and the same enzyme may exert diagonally opposite chemical effects if need be. The synthetic enzyme may act like a governor upon the metabolic machine of the cell. If the influx of utilizable substances is normal or subnormal it works synthetically and builds up protoplasm; if the influx is too great it reverses this state of affairs and breaks down protoplasm analytically. We are already very close to the view of the self-regulation of metabolism by reversible enzymes in the case of the liver glycogen, and of fat digestion and absorption. A simpler conception of glycogen metabolism cannot be held than that controlled by an enzyme which converts sugar into glycogen, when there is an excessive ingress of sugar, but reversely converts glycogen into sugar when there is an insufficient influx of sugar.

The metabolism of fat would be readily intelligible if we similarly accept the existence of an enzyme in the fat cells which would be capable by means of its reversibility of maintaining a definite equilibrium between the soaps in the blood and the fats in the fat cells, or which some enzyme (to apply the protothesis to fat digestion) were capable of

splitting up fat into fatty acids and soaps within the intestinal lumen, and after their absorption recombining them into neutral fats again.

The doctrine of an intracellular enzyme being active during normal cell growth brings with it the suggestion of a detriment to this enzyme when we are confronted with abnormal cell growth. No doubt the intracellular laboratories are seriously upset, and the anarchistic growth may be due to several possible factors:

1. The self-regulating catalytic mechanism of the synthetic enzyme may be destroyed; it can only build up, no longer decompose.

2. There may have preceded a lesion to the finer structure of the cell substance, a lesion though delicate, yet irreparable, paralyzing the self-regulating catalytic metabolism.

3. The normal tissue tension in the environment of the degenerate cell can hold it in check for a while if the lesion has struck only one or a few cells—the cell state is threatened by the leaven of rebellion, but perhaps the normal tissue equilibrium of the cell state may be restored if the anarchy has not struck too many cells; they may be forced to autodigestion, or some other form of disintegration, and for all that we know this may occur often if the cell state is vigorous and the metabolism normal.

4. But if the protoplasm apparatus of a considerable complex of cells is disturbed simultaneously, the normal cells in the environment, the tissue juices, etc., are helpless to overcome the excessive growth.

Some have argued that cancers always grow from out of themselves ("aus sicht selbst"—Ribbert); that is, one cancer cell always grows from a preceding cancer cell—until the original degenerate cell is reached. But I can conceive of no reason why the altered metabolism of large groups of malignant cells should not be able to produce such detriment, by chemically affecting adjacent normal cells, that their cytoplasm also receives a subtle damage, sufficient to paralyze the self-regulatory catalytic apparatus for growth (a kind of enzymatic, not bacterial infection). This extension of catalytic infection to other cells, even to the cells of the bloodvessels, is, of course, as yet an assumption; but it is well known that all the various tissues in an autonomous (Lubarsch) neoplasm are in a state of abnormal proliferation, particularly the bloodvessels which give evidence of a peculiar development (Klebs),<sup>1</sup> explainable only on the assumption that this tissue also has been drawn into the cell anarchy, but not to the same extent and character as the cells of the neoplastic parenchyma.

The cell has within its protoplasm certain recognizable structures which may be termed the organs of the cell, viz., the nucleus and its constituents, the chromatophores, centrosomes, the plastids—the passive

<sup>1</sup> Pathologie, Bd. xi.

bodies (E. B. Wilson), the metaplast or paraplast, the vacuoles, with their inclusions and secretions, the pigments in certain locations; all of these things signify that the cycloplasmic meshwork is not everywhere in the cell of the same chemical composition or reactive energy. This is already suggested by the fact that widely different reactions, sometimes chemically opposed to each other, occur in the same cell simultaneously. In the cytoplasm, synthetic and analytic transformations occur, not always by the same chemical reactions, but by a series of widely differing reactions. The decomposition of glycocoll to form urea, for example, is not conceivable without a liberation of the  $\text{NH}_2$  group from a part of the glycocoll molecule, then follows an oxidation of the remainder, and eventually a combination of the fractional parts. But it is essential that these reactions should occur in well-ordered sequence, otherwise urea cannot be formed in this way. A lawful and ordered sequence of this and numerous similar composite reactions within the cell necessitate the conception that the different agents work separately in different compartments of the cell, we are forced to accept a chemical organization which excludes the idea that the cytoplasm is everywhere the same chemically—in short, *there cannot be an ubiquitous chemical equivalence of protoplasm*. The colloidal reagents then are separated by walls, to them impenetrable and secure from their chemical influence. Let us conceive of a lesion, invisible to the microscope but destroying these partitions, and we can realize the danger of liberation of enzymes; they can now attack all elements formerly inaccessible, or they may even attack each other.

This is the proper place to be reminded of the many theories of the causation of cancer, attributing it to some form of irritation (to which the parasitic theory may be classed also) or to trauma.<sup>1</sup>

<sup>1</sup> Hemmeter. Cancer Etiology, Diseases of the Intestines, vol. i. p. 677.

It may be objected that I am here moving on very hypothetical ground, and having in the beginning of this article doubted the value of hypotheses, that I am myself now adding assumptions which go beyond the demonstrable state of facts concerning cell growth. But I must contend that I am not formulating a new hypothesis when I assume that all cell growth must be under the control of an intracellular catalyzer; I am simply for the time being using an assumption based on present observations, which, however, have not yet been sufficiently comprehensive. We know of the causal relation between cell growth, cell chemistry, and catalyzers. Certain reactions occur in the cell, certain products are built up, certain substances decomposed. We can isolate the synthetical and analytical products; we have in many instances isolated the enzymes and repeated their characteristic reactions in the test tube. We know from the nature of certain intracellular reactions that they must inevitably occur in separate compartments. Hence we are forced to believe that the growth of the cell structure itself is a separate and distinct performance, that there must be self-regulating cytoplasmic syntheses in the cell, and that in pathological cell growth this chemical process is deranged. I am here making temporary use of a "protothesis" (see W. Ostwald, *Naturphilosophie*, s. 399), with the view that further researches may instruct us whether the assumption is correct or not. The difference between a protothesis and a "hypothesis" is that the former adds nothing to existing observations which cannot further be tested. A protothesis is a temporary conclusion drawn from experience, observation, or experiment, for the purpose of subjecting it to critical testing concerning the limit of its value and significance.



**METASTASES.**—Virchow has expressed the opinion that malignant tumors may extend in three different manners:<sup>1</sup> First, by immediate propagation—that is, by direct extension or growing over from one organ into another; second, by dissemination—that is, detachment of tumor particles which settle down in another position; for instance, if a carcinoma of the stomach extends through or perforates into the peritoneum, the cells of the carcinoma may gravitate to any portion of the peritoneum and cause independent secondary growths. The third manner of extension is highly interesting from the standpoint illuminated in the preceding pages, and in order not to express the views of this great master in a wrong manner I will quote his own words: “This manner of metastatic extension makes it very probable that the transference occurs by means of liquids, and that these possess the power to create an infection (*‘Ansteckung’*), which causes the individual parts to form a reproduction of the same mass which was originally present.” Is it not possible that Virchow here conceived of a form of catalytic action? The other two forms of metastatic extension can, of course, not be denied. The third type, however, has been emphatically denied, and has not as yet been recognized by any pathologist of prominence.

It was Waldeyer<sup>2</sup> who first demonstrated by systematic investigation that carcinomas grow into the lymph spaces and vessels, and so may reach the general circulation. This observation has been abundantly confirmed; and, furthermore, the characteristic difference has been established that carcinomas readily grow into the lymph vessels, but that the bloodvessels offer them considerable resistance. (It is claimed by Hanse-  
mann that sarcomas, on the other hand, may readily break into the bloodvessels.) A number of prominent special investigators of this subject have called attention to the comparative rarity with which metastases occur by the way of the circulation, and Hanse-  
mann<sup>3</sup> suggests that a large part of the detached carcinoma cells are destroyed in the blood circulation.

It is essential to distinguish between the local factors which can be recognized as active in the development of a primary tumor and the general factors which determine its future fate, particularly the development of metastases. Of the local factors the most prominent ones have already been sufficiently considered, but the factors which control the formation of metastases are very manifold; and in this connection I should like to call attention to the following: (*a*) Condition of other organs; (*b*) abnormal states of the entire body, the simultaneous action or refusal to act of the regulatory apparatus of the organism; (*c*) acquired or inherited disposition, spoken of as individual disposition (the carcinoma dyscrasia). It is in this connection that the collective

<sup>1</sup> Cellular Pathologie, s. 258.

<sup>2</sup> Virchow's Archiv., 1867, Bd. xli.

<sup>3</sup> Loc. cit., p. 91.

investigation of the German government, under the direction of Prof. E. von Leyden, gives promise of throwing light upon the cancer etiology as far as it is associated with bodily constitution, vocation, inheritance, nutrition, manner of living, etc.

In this connection I desire to call attention to a possible explanation of the rarity of metastatic extension of cancers by way of the blood circulation. The idea was suggested by the investigations of Belfante, Carbon, J. B. Bordet, Ehrlich, and Morgenroth, previously referred to. Concerning the hæmolytic action of the serum of one animal upon the erythrocytes of an animal of another species, it is necessary that the effect of the serum of normal individuals upon isolated cancer cells of other individuals should be studied, for it is conceivable that the cancer cells represent forms of protoplasm which have become *so far alienated and emancipated from the general physiological laws of the body that they actually represent cells foreign to the body against which the serum brings into action its means of defence just as it would against any other foreign intruder*. This is, to my mind, a very hopeful direction for investigation, with a view to prospective prophylaxis or treatment. The point of inquiry will have to be: "*Does not the organism contain in its blood serum defensive substances capable of destroying cancer cells as long as they are not flooding the circulation in excessive quantities? and, if so, how can this natural means of defence be augmented?*" The fact that carcinomas extend preferably by the way of the lymph vessels is highly suggestive of the means of defence in the blood circulation above referred to.

CRITICAL RETROSPECT. In the preceding I have attempted to consider the pathogenesis of cancer from the standpoint of the chemist and physiologist rather than from the bacteriological standpoint. The principal hypotheses were referred to and the difficulties in the way of the acceptance of the parasitic theory briefly given. The changes which cells may undergo under normal and abnormal conditions were presented in the paragraph on "metaplasia." In order to narrow down the point of inquiry the investigations were made upon one type of carcinoma only—that with which the author has greatest familiarity—the adenocarcinoma of the stomach. A *résumé* of recent experiments on tumor transplantation preceded the writer's personal experiments, the main conclusion of which was that gastric ulcers can be experimentally produced, and that the edges of these gastric ulcers can be brought to undergo adenomatous transformation by the injection of a cell-free and sterile fluid obtained from a cancer of the same organ from the same species of animal.

Inasmuch as this filtrate was destroyed after being heated to 60° C., it was concluded that the agent active in causing this abnormal proliferation at the edges of experimental gastric ulcers was a catalytic agent. It might be objected here that the successful experiments were



too small in number to permit of reliable conclusions. On this point I wish to state that the experiments extended through years, and at times had to be given up entirely for five to six months for lack of material, because I believed that I could work only with cancer material developed spontaneously in animals, and that cancers even if produced experimentally in the method described did not contain the catalytic agent in sufficient quantity to cause adenomatous proliferation in other animals. The main reason for this is to be sought in the fact that the experimental adenomata are very small; in three out of four cases their recognition depended upon microscopic examination. Although I was and still am in communication with the principal veterinary schools of this country, and even with Professor Ostertag and Professor Regenhogen, of the "Thierärztliche Hochschule," of Berlin, I have come into the possession of only one dog with cancer of the stomach. The investigations would have been indefinitely delayed had I depended exclusively upon this material. At present I am still engaged with these experiments, and by the aid of Profs. Frank Martin and J. Mason Hundley, whose aseptic technique I hope will secure me a larger number of recoveries from the operations described, I hope to be able to report an additional number of successful experiments in the near future.

The fact that in one instance adenomatous degeneration identical with *ulcus carcinomatosum* developed at the edges of a pre-existing gastric ulcer spontaneously gives promise of a new source from which to derive canine cancer material. At the same time this spontaneous development of cancer may be interpreted as a criticism of my deductions. It may be argued that the injection of the sterile and cell-free cancer extract does not prove that an enzymatic agent is necessary to start already proliferating cells into a condition of malignancy, for this instance proves that they may pass over into that state without any extraneous agency. Upon closer consideration, however, this criticism can hardly be considered as invalidating the main deductions, for throughout our considerations I have not argued that something entirely extraneous to the cell is needed to cause cancerous proliferation, but, on the contrary, I have tried to emphasize that the agent is something which the cell contains or produces within itself, but its regulatory mechanism is destroyed, etc.

The adherents of the parasitic theory might argue that the cancer extract, though sterile, may contain the products of bacterial metabolism, toxins, etc., which are soluble and can pass through a Pasteur filter, and that it is these toxins which acted as the agency causing the abnormal growth. This objection it is impossible to meet. It might be urged, however, as far as we can judge from the infectious diseases, that bacterial toxins may after injection cause the clinical picture of the disease, but not the characteristic histological alterations in the cells

of the tissue which are concomitant with an infection by the living bacteria. Injections of tuberculin, for instance, cannot cause tubercles.

A possible objection is also found in the fact that adenomas of the digestive canal have been caused by mechanical injuries; for instance, by cutting off the lower ends of the glands of Brunner and of Lieberkühn. This observation has not as yet been satisfactorily investigated, and it has not been claimed that adenomas caused in this way were malignant. Lubarsch<sup>1</sup> succeeded in producing a fibro-adenoma in the liver by transplanting a portion of liver into an artificial lesion made in another region of this organ. He does not maintain, however, that this was a malignant—or, as he prefers to designate it, an “autonomous”—neoplasm, and presumes<sup>2</sup> that his experimental neoplasm would have eventually given way to a connective tissue cicatrix.

In the preceding it has been pointed out that the autonomous development of neoplasms (adenomas) may be due to subtle damage to cytoplasm, which is in fact another way of expressing the traumatic and irritation etiology of neoplasms. I do not wish to dispute such possibilities. On the contrary they are to a large extent necessary for the bringing about of deranged catalytic action already described. It is important to emphasize in this connection that I have not succeeded in producing an adenocarcinoma by cutting or bruising the gastric glands, not even when they were in the environment of a pre-existing lesion.

The studies concerning the effect of osmotic pressures upon normal and cancer cells suggest the influence of physical energies upon normal as well as abnormal cell growth, and that future investigations along this line even promise to throw light upon this problem.

The immediate and specific causes of cell division are next considered. The theories of Virchow, Thiersch, Boll, and Weigert are abstracted, and the conclusion reached that the stimulus to normal cell growth is of a chemical nature.

The influence of physical laws upon cell growth constitutes another paragraph, which is followed by a consideration of the question of how the cell builds up protoplasm, that is, the methods and means by which it carries on the synthesis of its own substance. It is here suggested that this is effected by means of intracellular catalyzers.

The conception of how the cell protoplasm must be constructed, its possible chemical organization, concludes with a support of the view accepting the foam structure of protoplasm, and of a special catalyzer regulating the synthetic construction of protoplasm.

As the cell is conceived to be made up of innumerable ultra-microscopic compartments, the more subtle and partial damage of cytoplasm and nucleus in disordering the orderly and normal performances of intracellular catalysis are next set forth.

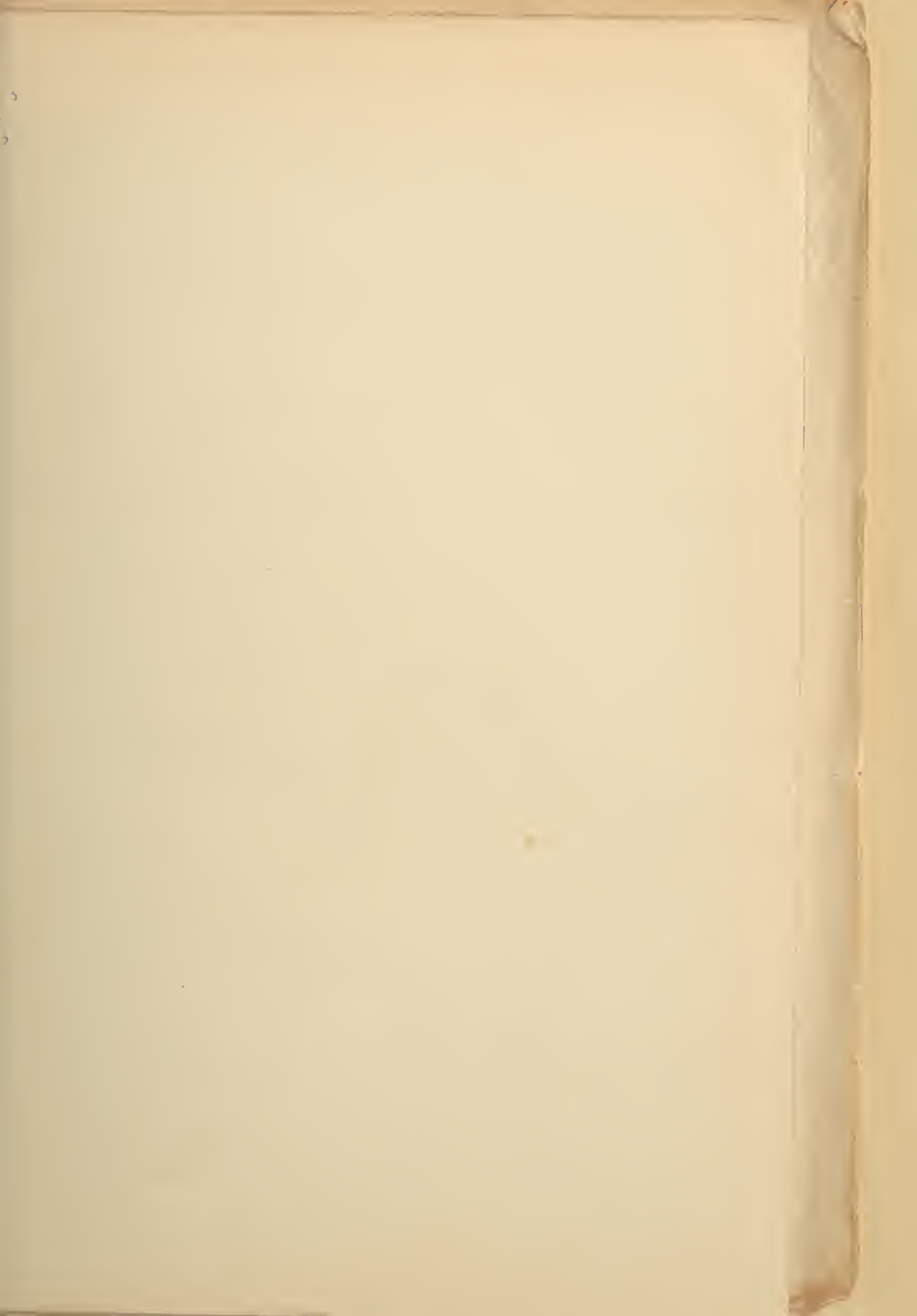
<sup>1</sup> Zur Lehre v. d. Geschwülsten, etc., loc. cit., p. 253.

<sup>2</sup> Loc. cit., p. 254.

The reversibility of enzymes is then briefly considered, and the possibility of a damage to the ferment which controls the upbuilding of protoplasm is suggested, and also that there cannot be ubiquitous chemical equivalence of protoplasm.

In the final paragraph on metastases the suggestion is thrown out that possibly the blood serum contains defensive substances effective in the destruction of cancer cells, and the study of this means of defence gives hope of a more successful form of treatment.

In speaking of the transformation which the edges of the experimental ulcer in dogs underwent after injecting the sterile extract of canine gastric adenocarcinoma I may have unwittingly designated them as "gastric adenocarcinomas." What I really mean throughout the article is not that a genuine gastric carcinoma had been produced in my experiments, but that such a histological transformation was effected that the microscopic appearance resembled that of a beginning adenocarcinoma. This expression is as far as the experiments justify me to go. I do not wish to imply that a typical cancer had been produced in this way, for this designation brings with it numerous attributes which it was impossible to bring into the experimental results. Above all things, I am not able to say whether the cell proliferation thus produced experimentally would have gone on to develop a genuine malignant tumor had the animals been permitted to live, or whether the proliferation would have been arrested and its place taken by a cicatrix. To complete the conception of carcinoma we must demand the evidences of malignancy, as is expressed in the production of metastases. Metastases were not produced in any of the animals examined. They occurred only in the dog in which a gastric ulcer had developed spontaneously.









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If we first of all turn on the current and then approach the electrode to the patient, when we arrive at a certain distance, sparks will pass which will be very painful. If, on the contrary, we first of all place the electrode in contact with the skin and then start the machine into operation, no sensation whatever will be perceived by the patient. And it is in this manner that we make our applications to the mucous membrane of the patient. We first place the electrodes in position and then start the motor, graduating the current until we reach the dose which we have determined to give in the particular case before us. In a like manner, at the termination of the treatment, we reduce the current to zero and stop the machine before we remove the electrodes from the patient. In selecting cases of hyperchlorhydria for treatment by this method, it is needless to remark that a sharp line must be drawn between those of purely functional nature and those due either to a chronic glandular gastritis or to the irritation of retained and decomposing food residues. It is, of course, only in the former that we can hope to ameliorate the condition of the patient by electricity. In my experience, cases of hyperchlorhydria, due to hypersthenic glandular gastritis, are aggravated by the use of high frequency electricity.

In the limits of this short paper it is, of course, impossible to go very deeply into the technic of the use of the high frequency currents in the treatment of affections of the stomach. Those who are interested in the matter will find the subject further elaborated in a small work which I have recently published.<sup>2</sup>

<sup>2</sup> "Manual of Intra-gastric Technic: Practical Lessons in the Use of Instruments in the Diagnosis and Treatment of Diseases of the Stomach." London: Glaisher. 1903.

*AN EXPERIMENTAL AND CLINICAL STUDY OF THE ETIOLOGY OF HYPERCHLORHYDRIA.*

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It is a well-known fact that the gastric juice of carnivora is much stronger in HCl than that of the herbivora. It may not be so well known that the gastric juice of a carnivorous animal can be made to contain a less amount of HCl by being fed upon a carbohydrate diet for a long time. Two dogs of the same litter (*a*) fed exclusively on milk, potatoes and rye bread, and (*b*) fed exclusively on beef, mutton, pork, fish and water. At the end of one year dog (*a*) fed upon carbohydrates had a gastric juice, one hour after a roll and a pint of water, containing 3 per 1,000 of HCl; dog (*b*) who was fed upon a meat diet had a gastric juice containing 6.540 per 1,000 HCl. These two dogs were raised in two entirely different families. Dog (*a*) was raised by a gentleman living in a country district, where meat was not easily obtained and milk was very abundant; dog (*b*) was raised in the city, and lived upon the refuse meats from the table. Unless conducted in this manner and watched by competent observers for a long time, at least one year, the experiment is of no practical utility. It is conceivable that we do not as yet know all of the constituents of the gastric juice; clinically, it has been very frequently observed that the secretion of the intestines may contain traces of products of metabolism and other toxins when the function of the kidney is suppressed or lost. The gastric juice of epileptics may contain toxic substances. Augustini, who recently investigated this subject, found that the gastric juice of an epileptic, when injected into the abdomen of a rabbit, proved fatal, with general toxic symptoms and clonic convulsions. This was especially true when the gastric juice was obtained immediately before or after an attack. Normal gastric juice was found to produce no such evil effects. Augustini concludes from these experiments that systematic lavage and disinfection of the stomach and intestines are indicated in all cases of epilepsy. What we wish to emphasize in this introduction to the consideration of hyperacidity is that hyperchlorhydria, although frequently a neurosis, is, in our opinion, occasionally a process of adaptation of the mucosa to the increased demand for work.

As far as diet is concerned, the hypersecretions do not exactly coincide with the hyperacidity in the treatment. For the augmented gastric juice in the super- or hypersecretions may be a passive act on the part of the glands—their activity may be kept up by retained food. But in hyperacidity the excessively high percentage of HCl is an active process, an irritative state of the mucosa in which it responds with excessive formation of acid to all



food stimuli. In the hypersecretions the diet should be selected with regard to favoring rapid gastric evacuation. In hyperacidity there is no better diet than rest. These are states in which there is an accelerated digestion of albuminous and proteid foods, and a retardation of carbohydrate digestion, which is caused by an inhibition of the inverting action of the diastase of the saliva, the ptyalin, by the excessive amount of HCl. The same is true of the pancreas diastase. Boas has shown that a neutralization of the chyme will restore the diastatic action, but we have assured ourselves that if the gastric acidity has once reached 0.3% the action of the ptyalin cannot again be so perfectly restored by neutralization with sodium carbonate as it was before. In other words, excessive hyperacidity permanently damages the ptyalin. It may resume some inverting action after neutralizing, but it is not equal to that it evinced during the first forty-five minutes of normal gastric digestion. An intensely acid gastric juice will produce a deleterious effect on the bile by precipitating from it a substance up to the present time not isolated, by which it effects partial digestion of the fats. In a similar way the secretion of the pancreas is prevented from performing its work, because it can do so only in an alkaline medium. There are three organic diseases which dietetically come under this group of excessive acidity or secretion; these are ulcer, gastritis acida, and *ulcus carcinomatosum*. Concerning the dietetic treatment of hyperacidities, uniformity of opinion does not exist. As a general rule, it can be stated that in the simple forms a bland, unirritating diet, which at the same time binds as much hydrochloric acid as possible, should be prescribed. We are in favor of a diet that does not irritate the mucosa any more than is absolutely necessary. There are two indications: (1) An etiologic one, directed to the condition of the mucosa and demanding rest for the irritative state present. (2) A symptomatic one, directed to neutralization of the excess of HCl by diet having the greatest HCl-binding affinity. These two indications are to some extent opposed to one another. The etiologic indication necessitates avoidance of albuminous food, for in our experience proteid and albuminous foods produce an increased secretion of HCl. The second or symptomatic indication calls for a large ingestion of albumen to combine with the HCl. In case of ulcer the food must be the least irritating, the mildest that our *ménù* contains. Not the total quantity of acid secreted constitutes hyperacidity, but the amount secreted in *excess* of what is *required* for combining with the proteids. For instance, a case may show hyperacidity after a simple Ewald test breakfast of a roll and a glass of water, because the acid secreted has nothing to combine with and remains free, whilst the same case may show very little excess or normal acidity after the first of our double test meals, as employed at the Maryland University Hospital, consisting of beefsteak, eggs, rice, milk and bread, because the acid, in this instance, at once enters into combination. The more abundant secretion of HCl is more completely



used up when the meals consist of a preponderance of proteid food than when they consist of carbohydrates. Therefore, the dietetics of these cases, as usually recommended, include the red meats, venison, game, turkey, eggs, chocolate, etc., liberally, a certain limitation of carbohydrates and the alkaline carbonated waters. In hyperacidity and supersecretions spices are to be forbidden, and only so much salt as is indispensable to make the food palatable. All acids, such as vinegar or lemon juice, in the food simply aggravate the trouble.

There are undoubtedly different kinds of hyperacidities. We feel justified in distinguishing two classes: (1) Those in which there is a preponderance of nervous symptoms and fragments of the mucosa show no increase in the number of gland tubules or in the oxyntic or acid cells; these cases are, then, of a purely neurotic type.

(2) Secondly, those in which there is an increase in the number of gland tubules or in the oxyntic cells. There is no hard and fast line to separate these classes, but they demand somewhat different treatment. A number of competent observers have recommended an exclusion of proteid and an increase of the carbohydrate foods in hyperacidity.

For, although proteid foods combine with more HCl than any other, they are also the greatest stimulants to the secretion of acid. See Dujardin-Béaumont ("Traitement des maladies de l'estomac") and von Sohlern (*Berlin. klin. Woch'schrift*, XCI., Nos. 20 and 21); Fleiner (*Volkmann's klin. Vortr.*, No. 103); Rummo (*Therapia clin.*, 1892, Nos. 10, 11, 12); v. Jaksch (*Zeitschr. f. klin. Med.*, Bd. XVII., 1896). These writers argue that carbohydrate food is not so irritating and calls forth much less secretion of HCl. W. Roux ("Entwicklungsmechanik der Organismen," 1895) states that increased activity heightens the specific force of the organs, whilst diminished activity lowers it. The existence of the cells of the organism depends upon their work; those that work most are nourished best and grow strongest. In other words, the elements in any tissue that are incited to greatest activity and function will gain supremacy over others and increase in strength and numbers. The deductions are not purely theoretical, for not only do we find proliferation of acid cells in hyperchlorhydria to be present in from 50 to 75 % of the cases, but in animals with a high acidity of HCl (dog, fox, wolf, etc., carnivora) there is a tremendous multiplication of acid cells. It seems logical, therefore, that there are cases in which the hyperacidity may in the long run be kept up by proteid diet, although for the time being this diet may render the acidity less by combining with the free HCl. Experience teaches that the most annoying symptoms, the gastralgia and pyrosis, are promptly relieved by the proteid diet, and we shall endorse the latter as most eminently proper in selected cases. When, however, the symptoms are relieved only very briefly, particularly when the ratio of the ethereal to the preformed sulphates in the urine is found to become very

high under a rich albuminous diet, and the indican increases, we advise a diet rich in carbohydrates and fats. This can be filled by all breads and articles made from flour, rice, peas, beans, potatoes, the cereals, oatmeal, and rich milk and butter. It is true that in some forms of hyperacidity these substances can be found sometimes six hours after they are ingested, unchanged in the stomach; here the motility is seriously at fault. As alkalis must be given even with a proteid diet, they should, in case the food consists largely of carbohydrates and fats, be given immediately after meals and combined with ptyalin or diastase to hasten amylolysis. It is frequently observed, however, if the amylaceous diet is persisted in that the free HCl becomes less and less and the alkalis and ferments may be dispensed with. This diet we suggest particularly after the albuminous diet has failed, for there are cases of hyperacidity which are undoubtedly maintained by an exclusive proteid diet. It must not be overlooked that such a thing as a *pure* carbohydrate diet does not exist, because all articles of this class contain protein, and some very considerable quantities of it; peas, beans, and lentils, for example, contain more protein than beef, ham, or fish. It is not a total exclusion, but simply a reduction of proteid that is practically recommended.

All cases of hyperacidity require a certain amount of carbohydrates. It is a matter of experience that proteid diet alone will not permanently satisfy their cravings. Flour and the many articles prepared from it are not readily converted into dextrin in an excessively acid medium. It is expedient, therefore, to recommend dextrinized flours, such as Avenacia, Maggi, and Kuffe's flour. The American product, "Horlick's Food," is a flour in which the wheat starch has been almost entirely converted into dextrin by malt diastase. It has a high caloric value, and its price is sufficiently moderate for humbler practice when artificial flours seem indicated.

In the hyperacidity of ulcer, the diet must be of the least irritating quality, and the coarse-fibered meats—beef, mutton, lamb, veal, venison—are not to be allowed, even during the periods of convalescence, and when they are finally conceded, they should all be reduced to a pulpy (scraped) form.

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### THE TREATMENT OF HYPERCHLORHYDRIA.

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of Chicago.

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IN consideration of the subject of treatment of hyperchlorhydria, we must have some conception of the condition which we treat. It may be well to call attention to the generally recognized fact that hyperchlorhydria is a symptom of a disturbed function, characterized by an increase in the formation of hydrochloric acid. There is a strong inclination among

clinicians in this country to classify hyperchlorhydria almost entirely among the neuroses of the stomach, and since the more recent experimental work of Pawlow<sup>1</sup> has shown the psychic character of the secretion, there is stronger disposition to retain this classification of a special nervous disturbance. In Europe, Ewald has long ago shown the nervous origin of hyperchlorhydria in many cases. Reichmann dignified this to a special secretory disorder, and his observations were confirmed by von Noorden, Jaworski, Sahli and others.

The primary ultimate cause of these symptoms of increased secretion of gastric juice, or rather HCl during the process of digestion, is regarded as far from settled. So long as we are more or less equally ignorant of ultimate factors, we may be pardoned for venturing a few personal observations to compare with those others have made. As stated before, many regard it as some form of secretory neurosis. When we use the word *neurosis* we do not add much to the clearing up of the subject. Neurosis is not definite. Is the lesion in the Meisner plexus, a ganglion or in the spinal cord? The word neurosis applied to hyperacidity, hyperchlorhydria, or superacidity, is, therefore, at present synonymous with symptom. Therefore, if such it really is, no amount of clinical bolstering can dignify it into a "disease," any more than ascites can be so regarded.

Strümpell<sup>2</sup> is very doubtful if such a thing as psychogenic dyspepsia exists; admits many cases of psycho-therapy being efficient, but prefers "functional dyspepsia" to the term "nervous dyspepsia." Boas was not certain that we could call these cases acid gastritis, because the increased formation of acid is only one of the numerous symptoms of the inflammation. This increased formation of acid may be of short duration, may be intermittent, or follow a period of hypoacidity.

Pawlow<sup>3</sup> has shown experimentally that in the diseased state the gastric secretion assumed an unusual and special character. The quantity at first markedly exceeded the normal, but later an exceptionally steep decline set in; which confirms some of the author's earlier observations. Cohnheim,<sup>4</sup> reporting on Pawlow's more recent research on stomach secretions following acute gastric catarrh produced by the application of heat and cold, finds that the mucosa secretes an alkaline mucus instead of the acid gastric juice. After subsidence of the catarrh, there follows a period of hypoacidity, followed by a period of hyperacidity, before the restoration of normal conditions.

Beginning with the paper read before the International Medical Congress, Rome, 1894,<sup>5</sup> the author has repeatedly pointed out that inflammation of the gastric mucosa was attended at the onset by an increased flow of hydrochloric acid, to be followed later, if the process continued, by a decrease in the activity of the gastric glands. In the paper referred to, it was stated that nitrate of silver and tannic acid increased the flow of hydro-

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*Histological Character and Diagnosis of  
Malignant Neoplasms of the Digestive  
Organs and Peritoneum.*

BY

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FROM

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES,

JULY, 1903.





## HISTOLOGICAL CHARACTER AND DIAGNOSIS OF MALIGNANT NEOPLASMS OF THE DIGESTIVE ORGANS AND PERITONEUM.

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THE progressive enlargement, not restricted by any obstacle, and the destructive or corroding advancement of malignant growths have given rise to the impression that cancer cells possess peculiarities of growth not found in other neoplasms. It has been suggested by Hanseemann and others that the cells, through the proliferation of which malignant tumors arise, had undergone a change in their biological character. Many efforts have been made to obtain a clear conception of this change of quality, but they have not been successful. Hanseemann speaks of an antecedent change in the biological character of the cells, which is claimed to be necessary for pathogenesis of malignant neoplasms, but he does not define this change. In other words, an unknown, indistinct hypothetic factor is introduced, with the hope of clearing up our understanding of the origin of malignant neoplasms. It is evident that nothing is gained by attributing the pathogenesis of such growths to a change in the cells when this change itself remains incomprehensible and undefined. Ribbert<sup>1</sup> believes that the physiological processes of growth are sufficient to serve as guiding lines in the development of neoplasms. Hanseemann has attempted to make the stronger ability to grow comprehensible by assuming that the cells lose their characteristic peculiarities, a loss of their cellular individuality, whereby they are assumed to revert to a less differentiated stage, approaching again a condition more like the cells of the ovum. This reversion or change of cells he calls "anaplasia"—(to build backward) undifferentiation. Hanseemann based his conception upon deviations of tumor cells from the character of the normal cells from which they originated. Frequently the neoplastic cells show a simpler morphological quality and structure, which he interprets as a lesser degree of differentiation. For example, pavement epithelium loses its tendency to become hard or horny-like epidermis, and in cancers may represent morphologically indifferent cell forms. But this simplification of the structure of tumor cells is frequently not found in cancers. For example, the pavement epithelium of the epidermic cancer may

<sup>1</sup> Pathol., s. 6, 10.

show extensive cornification in the lymph glands and secondary metastases, and is indistinguishable from the epithelium of the primary seat of origin. The cylindrical cell carcinoma may form mucus in the secondary nodules. The osteosarcoma produces calcified bone substance in the metastases found in internal organs.

The anaplasia of Hanseemann becomes less and less evident the nearer the neoplasm is traced to its beginning stages, that is, in those stages where it would count most as an etiological factor it is less evident. In order to be considered a cause it should precede the development of a neoplasm, not follow it. Ribbert considers the anaplastic changes as secondary, as a reversion. Hanseemann holds that new cells, peculiar to themselves, arise by this process. This is denied by Ribbert, who interprets it as a reversion to a previous stage in development.

Hanseemann<sup>1</sup> first used the word "anaplasia" in 1890, the prefix being *ana* (from *ava*, backward, and *πλάσσειν* to build, building, "zurück," "backward"). He understands by it a condition in which the cells have lost, in part, their specificity, have become "entdifferenziert," so that they have acquired the property of independent existence, have lost what he calls "altruismus." He conceives that this anaplasia is brought about by abnormal, especially unsymmetrical, mitoses, and that some of the *idioplasm*<sup>2</sup> is thereby lost, while idioplasm which had previously been in the background now comes to the front.

Hanseemann does not consider the anaplasia in itself sufficient to produce malignant neoplasms, but emphasizes that a special factor, agent, or irritant is necessary in addition to cause the anaplastic cell to proliferate into a tumor. This agent has been supplied in the argument of those who hold the view of the parasitic origin of cancer. The efforts to demonstrate characteristic bacteria as causes have been in vain. The protozoa have been blamed as the cause of cancer, but most careful researches of many competent observers have resulted in the consensus of opinion that the curious enclosures thought to be protozoa are degeneration products of cells and nuclei enclosed by leucocytes and lymphocytes.

It is a characteristic of malignant tumors that cells of other types than the original are never involved in the growth—a pavement epithelial cancer never involves cylindrical epithelia. This necessi-

<sup>1</sup> Virchow's Archiv, Bd. exix. p. 321.

<sup>2</sup> *Idioplasm*. In biology a term introduced by Nägeli for a special hereditary reproductive substance not contained in the body of the cell, but in the *chromosomes* of the nucleus controlling and determining the *actual* characters of the particular cell, and also those of all of its descendants. Each idioplasm is composed of several or many *ids*, which are capable of growth and multiplication by division; although much smaller in bulk than the rest of the living substance of the cell or body (*trophoplasm*), idioplasm is the active element in the process of formation, and determines the detailed construction of the trophoplasm, which is the passive element.—Gould's Dictionary of Medicine.

tates the assumption, if we adhere to the bacterial hypothesis, that every kind of malignant tumor must have a particular species of parasite as its cause. Our understanding of the pathogenesis of tumors is made difficult by trying to apply the bacterial theory in its explanation.

A schema which should indicate that a neoplasm which corresponds to a certain type is benign and another that looks different is malignant is a conception that becomes impossible with closer and careful study of their growths. We should never approach a tumor with the question, "Is it a carcinoma or a sarcoma?" But the diagnosis should be developed like that of the disease in the living subject. First, we must consider the anatomical properties; second, the topographical; third, the distribution of the various tissue types in the tumor, and, fourth, the properties and peculiarities of the cells. Then, if at all, the diagnosis follows naturally of itself.

If the question is to make a diagnosis from a fragment of an organ separated from the body, we must first ask ourselves the question, "Is this a real tumor or is it an inflammatory proliferation, a simple hyperplasia, or infective tumor?" Theoretically it would seem easy to distinguish the inflammatory tumor from neoplasms, and yet there are cases where considerable difficulties arise, and, indeed, a confusion may occur in two ways: first, when a real neoplasm is taken for an inflammatory proliferation; second, when the latter has the appearance of a genuine neoplasm. The first danger is most easily avoided by very careful and thorough observation. It often happens that the stroma of the tumors is developed so greatly or infiltrated with small cells to such a degree that the real parenchymatous islands are only discovered after a protracted search. This is on record as having occurred with the scirrhi, which for a long time were classed with the fibromas or inflammatory thickenings.

Hansemann gives an interesting description of sections made from excisions of the vaginal portion of the uterus. The preparations gave a strong impression of a granular proliferation strongly infiltrated with cells. Newly formed vessels were everywhere present, which were filled with leucocytes, and the whole picture was flooded with leucocytes to such an extent that at first nothing was seen but these. It was only after a more thorough examination that he found groups of cells rich in protoplasm which were in several places arranged like epithelia, and were very different from the swollen endothelia. Without doubt it was a cancer.

The cancerous portions are also easily overlooked in old indurated ulcers, and a long series of preparations must first be made before we can arrive at a certain diagnosis. It happens much more easily that inflammatory neoplasms are considered malignant tumors.



#### 4 HEMMETER: NEOPLASMS OF DIGESTIVE ORGANS.

Both epithelia as well as connective tissue substances may form such great proliferations by means of inflammatory changes, which may show such a cellular composition that considerable practice and experience are necessary not to confound these with cancer and sarcoma.

In January, 1900, I came into possession of a specimen of intestinal tissue from a case of intussusception. At the tip of the invaginated part there was a circular swelling almost as thick as a finger, which might have been mistaken for a malignant tumor, and consequently as the cause of the invagination. The microscopic examination showed this not to be the fact. The thickening consisted of plentiful connective tissue with elastic fibres and fatty tissue. It was manifestly a case in which the intestinal wall and the serosa were thickened by inflammation.

Extreme difficulties arise when the endothelia have led to especial proliferation. It very often occurs in simple inflammation in various portions of the body that these cells increase to such a degree that the microscopic image shows a distinctly alveolar construction. This is found especially often in the pleura if a thick callosity is formed. But I have observed this alveolar structure in a benign neoplasm of the ileocaecal valve, and in one of the ileum. Whether at this place the mass of the cells take their origin from the epithelia of the pleura or intestine, or from the lymph-endothelia, has been the subject of much discussion. This point Hansemann does not consider as yet decided. They have, however, often been considered tumors.

In this connection two interesting cases are described by Hansemann. In both cases trauma had preceded. In one case the cheek had received a blow from a beam, in the other a rusty nail had penetrated the hand and remained there for some time. In the course of the succeeding weeks a small tumor developed in each case, and these tumors were very similar. They consisted of large spindle cells and round cells, rich in protoplasm, with tender intermediate substance, scanty stroma, and very abundant pigment. In the tumor of the cheek the pigment lay everywhere between the cells, and, therefore, arose from the bleeding caused by the blow. In the other case, however, the cells had taken up the pigment, and thus a complete similarity with a melanosarcoma arose. However, the pigment had one property which is not observed in melanosarcoma, it had a strong iron reaction, and, therefore, it was reasonable to assume that the pigment arose from the rust of the nail, and had been taken up by the cells. The simple extirpation of both tumors caused a permanent cure.

Proliferations of the connective tissue may not only have the appearance of real tumors, but inflammation may accompany the pro-

liferation of the epithelia. Friedländer has devoted a noteworthy treatise to these, and characterizes this growth of the epithelia as an atypical proliferation. They are found extremely frequently in the various chronic inflammatory processes of the epidermis, which also accompany proliferations of the connective tissue and the formation of granular tissues. The border of the epithelium grows deep down into the granular tissue on the edges of chronic cellulites of old ulcers, in lupus, etc., branches off in different ways, and finally forms lumps and nests of epithelial cells. They contain many mitoses and also often pathological and atypical forms. In many cases the similarity to cancers may thus become so great that a mistake may very easily be made. Hanseemann<sup>1</sup> has seen cases in which a differentiation from real cancrroids was no longer possible in the coarse structure of the proliferations and in which the clinical development demonstrated its nature. In other cases the diagnosis was made possible at once by the knowledge of the condition which this investigator designates as "anaplasia." Hanseemann takes this opportunity to point out especially the similar state of affairs in the larynx and at the vaginal portion of the uterus. Proliferations of the epidermis are often found so extended in the larynx, especially in tuberculosis, more rarely in syphilis, that the perfect structure of cancrroids is formed. If, in such cases, the entire larynx can be sectioned, tubercles will always be found somewhere, which will render the diagnosis possible. If, however, only an excised specimen is at hand during the examination, the diagnosis becomes extremely difficult, or even impossible. (At the vaginal portion of the uterus the so-called erosions may cause a similar confusion. These do not consist of wound surfaces, as has been heretofore assumed, but of islands of cylindrical epithelium which has forced itself from the neck of the uterus between the normal pavement epithelium of the vagina. Such conditions are found in small children, and are probably inherited.) Later on, if inflammation arises here, or if the vaginal portion of the uterus is injured during birth, the cylindrical epithelia sometimes grow downward like a hose and assume a striking similarity to destructive adenomas, into which they may really develop. On this account it is the more important to know that certain histological proliferations exist which bear the greatest similarity to cancers, and yet are not cancers. It is very probable that all these cases of cancrroids said to have been cured by internal remedies are such atypical proliferations of the epithelia.

**TUBERCULAR TUMORS.** Infectious tumors of the stomach and intestines are occasionally confounded with sarcomas. As a rule, it is not difficult to differentiate an intestinal retroperitoneal or omental tuber-

<sup>1</sup> Mik. Diag. d. Bösartigen Geschwülste.

cular tumor from a sarcoma. Yet I have seen cases where such tuberculous masses acquired such an extent and showed such a structure that they are not unlike sarcomas. Virchow himself at one time classed tuberculous tumors of cattle (*perlsucht*) among the sarcomas, on account of their fibrous structure, their cellular development, and their frequently scanty caseation. Similar *perlsucht*-like knots, resembling bovine tuberculosis, sometimes occur in man in the peritoneum and the pleura.

Hansemann<sup>1</sup> described two pulpy retroperitoneal glands, as large as the fist, without tubercles, with a minimal caseation and few tubercle bacilli. The characteristic giant cells are probably seldom found wanting in these affections. Tubercle bacilli are also present, but often in such small numbers that they are not discovered under the microscope. The transmission, however, usually succeeds on guinea-pigs, which in such cases always succumb under the form of tuberculosis peculiar to them.

ACTINOMYCOSIS of the stomach and intestines may present tumors at the operation or at autopsy which outwardly may simulate malignant neoplasms, but microscopic examination, as a rule, shows the characteristic structure (globules) of the fungus *actinomyces*.<sup>2</sup>

TYPHOID PROLIFERATIONS. If the neoplastic indurations of enteric fever (abdominal typhoid) should be encountered at operation or necropsy, they can be recognized without difficulty when fragments thereof are examined under the microscope. Only in cases of lymphoma of the liver might a possible confusion with malignant tumors arise.

The purely lymphatic character of the same characterize them well enough to distinguish them from sarcomas; they might possibly be confused with leukæmic or syphilitic proliferations. Sometimes melanosarcoma in the intestines forms similar ulcers of a strongly gummatous appearance, like typhoid in its early stages. If the amount of pigment contained in them is considerable, this alone suffices for a macroscopic differentiation. These melanotic proliferations also are not confined to the Peyer's patches and the follicles. Otherwise, however, the histological appearance of these sarcomas is so characteristic that they cannot easily be confused with the lymphatic proliferations of typhoid fever.

The gland tumors of the plague have recently been thoroughly investigated by Aoyama, and his investigations have been confirmed by Hansemann. The clinical progress of this disease probably rarely necessitates a differential diagnosis between these tumors and sarcomas. It is well known, however, that in all epidemic diseases, and especially at the close of an epidemic, rudimentary cases of plague occur which

<sup>1</sup> Loc. cit.

<sup>2</sup> Hemmeter. Diseases of the Intestines, vol. ii. p. 108.



may then lead to difficulties in the diagnosis. According to Aoyama and Hanseemann, the buboes of the plague show a proliferation of all three component parts of the lymphatic glands—of the lymphocytes, of the endothelial and of the connective tissue lattice-shaped cells. At the same time great hyperæmia, accompanied with hemorrhages, exists at first. Later on necrosis occurs in the tissue, and also suppurative softening. Finally the glands may become fibrous, hardened knots. The bacteria are present in great numbers in the glands, and may easily be detected by means of aniline colors, but not by Gram's method. Generally we are confronted with tumors which are not unlike typhoid lymph glands, only of an excessive size, and which can easily be distinguished from malignant tumors by their histological structure.

In a report from the United States Treasury Department, entitled "Bubonic Plague," by Walter Wyman, Surgeon-General Marine Hospital Service, it is stated (page 36) that intestinal plague is very rare, and Dr. H. F. Müller, in his valuable monograph "Die Pest,"<sup>1</sup> states that the anatomical changes in the digestive tract are not important in this disease. The mesenteric and solitary glands may be swollen, but they never acquire the size of deserving the name of tumors. In the stomach there are superficial hemorrhages. Wilm<sup>2</sup> describes the solitary follicles as swollen and reaching the size of a bean. The Peyer's patches were hyperplastic but not ulcerated. It is evident from these quotations that even in countries in which the plague occurs epidemically it rarely effects striking changes in the digestive tract, and should they occur they are not likely to be confused with malignant neoplasms.

LEUKÆMIA, PSEUDOLEUKÆMIA, SYPHILIS. These diseases may present difficulties for the differential diagnosis from malignant neoplasms. They may all give rise to the formation of large tumors. Leukæmia and pseudoleukæmia do not differ from each other in the microscopic pictures of their tumors. In both the tumors of the lymphatic glands are composed of typical lymphatic cells. However, the follicles, the proliferating centres of the lymphatic glands, have disappeared. The cells are slightly larger than the normal lymphocytes and show numerous mitoses of the typical form of the lymphocytes. Also in the infiltrations of the tissues of the kidneys, spleen, liver, and testicles the typical lymphocytes are everywhere found. Growing over into neighboring tissues and spreading out beyond an organ by means of propagation, they are never observed, and the constituent parts of the infiltrated organs are not destroyed, but only pressed asunder mechanically. It is for this reason that a liver or a kidney

<sup>1</sup> Nothnagel's Spec. Path. u. Ther., Bd. v. p. 41.

<sup>2</sup> Hygen. Rundschau, 1897, p. 222.



that has been completely infiltrated by syphilitic neoplasms, for instance, may yet function completely, and that neither uræmia nor jaundice usually appears as a result of the leukæmic proliferations pure and simple.

The ordinary syphilitic gumma of the gastro-intestinal canal (Fig. 1) can usually be distinguished without any difficulty from sarcomas, even



if they have assumed considerable proportions in the liver, lymphatic glands, or at other places.

Difficulties may arise for the macroscopic, but not for the microscopic, examination, which reveals either the typical granulation tissue, if it is in a fresh condition, or if retrogression has set in it shows a caseous and fatty detritus surrounded by strongly marked cicatrices. A number of German pathologists have described a syphilitic sarcoma (sarcoma syphiliticum, see Hanseemann, loc. cit., s. 194), the diagnosis of which is more difficult, since the clinical development is very similar to that of a malignant tumor. Beginning at one place and afterward appearing at others, recurring after extirpation, its frequently great resistance to syphilitic remedies—all these puzzling factors should cause the histologist to approach these tumors with a critical conservatism. Macroscopically the extensive fat metamorphosis and the caseation are very noticeable. And even if all the tumors are not in this state of regressive metamorphosis, there are nevertheless some which are thus constituted, and which finally break up entirely into a fatty pulp. Those places which still remain usually show the perfect structures of a soft large-cell sarcoma, in which the very abundant, finely reticular tissue strikes the eye, and in which the larger cells are embedded somewhat loosely, so that they can be brushed out to a certain extent. At the same time single tumors can usually be found which do not possess this great cellular development, and which appear as typical gummas. From this it follows that, after some practice, the case as a whole will be recognized as syphilitic, but that single extirpated tumors often do not permit a diagnosis which consequently reaches only a certain degree of probability. Naturally only the large round-cell sarcomas can give rise to error, not the spindle-cell sarcomas, the melanosarcomas, and the sarcomas with a specific parenchyma, as the osteosarcomas, chondrosarcomas, gliosarcomas, and those with giant cells. It is stated by some authors<sup>1</sup> that cancer-like formations may also arise from syphilis, or that there are actual syphilitic cancers. Hanseemann denies this altogether, and asserts that these carcinoma-like developments could only be cases of atypical proliferations of the

<sup>1</sup> Hanseemann. Loc. cit.

FIG. 1.—Syphilitic neoplasm of the stomach (from Hemmeter's *Diseases of the Stomach*, 3d edition). The superficial columnar epithelium and that of the vestibules and upper gland ducts is entirely lost. Enormous small round-cell infiltration has forced asunder the fibres of the muscularis mucosæ at A, A. At N and D the round cells have accumulated in large nodes extending from the muscularis mucosæ through the remnants of the glands. The gummatous nodule to the left of the illustration has broken down into a pale homogeneous non-staining granular débris. At B large bundles of muscle fibres are forced up into the glandular layer by distorting infiltration and proliferation. Within these bundles are contained numerous small arterioles at C. A few remnants of the gland ducts in a state of necrobiosis are visible at G, G. M. Muscularis mucosæ.



FIG. 2.  
enormously hypertrophied  
pyloric sphincter



epithelia in syphilitic ulcers or tumors. The relatively frequent occurrence of real cancers in individuals who are or were syphilitic, he assumes to be only a chance coincidence.

It is evident from the above (Fig. 2) that the exclusion of infectious tumors is not always an easy matter, but let us assume that these have been excluded, and we find that we are dealing with a real tumor, the most important question arises for the examiner, "Is the tumor malignant or not?"

The most reliable criterion of malignancy is the metastases. We must, above all, hold to that idea of malignancy which is given by the occurrence of metastases, and bear in mind that the metastases may commence before separate knots have been formed, distinct from the primary tumor, but according to Hansemann, we may speak of metastases even when single, viable cell groups have separated from the primary proliferation and lie embedded in the deeper tissue, that is, when the tumor has become *heteroplastic*, in the sense of Virchow. (Heteroplasia, from *ἕτερος*, other, and *πλασις*, shaping, meaning the presence of tissue or cells that may or may not be normal in a part where they do not normally belong.) But even this is not necessary for the diagnosis of gastric malignant neoplasms. On the contrary, it is sufficient if it is proved that the proliferation has broken beyond the boundaries of the starting tissue (gland cells in adenocarcinoma) downward. To be sure, it is hard to determine in many cases where the boundaries of many organs are to be looked for, since these boundaries may be displaced with the increase of the proliferation. A sarcoma of the tonsils and of the lymphatic glands has gone beyond the boundaries of the organ when it grows into the muscular tissue; a sarcoma of the bone-marrow has done the same when it has pierced through the bone. But a wart on the skin grows not only upward and outward, but also downward; it displaces the lower boundaries of the epidermis, and yet it is not a cancer. We should rather keep here to the criterion of the disintegration of the neighboring parts. If the epithelia possess a *membrana propria*, this disappears. The lymph spaces approach the tumor cells in an entirely open manner, and it can be seen that these heteroplastic cells are pressed into the lymph spaces. This crowding of heteroplastic cells into the lymph spaces and the ensuing new formation of connective tissue and vessels give rise to the alveolar structure—beneath the original surface. This heterotopia has already been emphasized by Virchow,<sup>1</sup> and is considered the most deciding

<sup>1</sup> Virchow's Archiv, Bd. iii.

FIG. 2.—Hypertrophic stenosis of the pylorus from chronic syphilitic gastritis. Section through hyperplastic pylorus and comparatively normal duodenum.



factor in the diagnosis. While I agree with Ribbert and Hansemann in assigning considerable importance to metastasis as a criterion of malignancy, I do not wish to uphold this phenomenon as an invariable test, for even benign tumors, myomas, and chondromas have been known to form metastases.<sup>1</sup>

The most experienced teachers of pathological histology advise examination of the tissue first with low powers of the microscope. In examining sections of neoplasms of the gastro-intestinal tract, the *muscularis mucosæ* is, as a rule, my landmark. Any proliferation of epithelial cells around a gastric ulcer, for instance, which has extended downward along the peptic ducts and broken through the "*muscularis mucosæ*" I am in the habit of considering malignant. At the same time I admit that gastric adenocarcinoma may develop from cells normally located, and that dislodgement of cells from their normal site is not necessary for the origination of such a cancer, though it may be the rule.

Hansemann asserts that by a study of the pathological reversion in neoplastic cells, which he has termed "anaplasia," it is possible to recognize malignancy in the absence of heterotopia. In the following I shall try to represent the characteristics which he conceives are essential to make up anaplastic cells. He has undoubtedly merited the gratitude of pathological histologists for having first called attention to the "undifferentiation," though it is occasionally not observable in the original or mother tumor, and in my experience, as a rule, becomes evident, if at all, in the metastases. It is well to bear in mind that during anaplasia no new kind of cells are developed which might be considered peculiar to themselves, but that it is essentially a return or reversion to a stage of earlier development, from which Ribbert believes<sup>2</sup> that they develop still further in the direction of embryological growth. Pathological reversion to an embryological state and anaplasia have the same significance for proliferation of tumor cells. Concerning Hansemann's statement that malignant tumors of the stomach have occurred which caused death and no heterotopia was recognizable microscopically, I must say that in a very large experience with gastric malignant neoplasms no such case has come to my observation. All gastric malignant tumors examined at operation or autopsy by myself showed heterotopia.

The most difficult histological diagnosis of stomach tumors has, in my experience, been encountered in deciding between chronic hyperplastic gastritis and scirrhus. On two occasions I was unable to make this differentiation from pieces excised from gastric neoplasms during operation. In one case operated by Dr. L. McLane Tiffany the gastric

<sup>1</sup> Lubarsch. Zur Lehre v. I. Geschwülsten, p. 263.

<sup>2</sup> Pathologie, s. 613.

neoplasm was not larger than the size of a half-dollar, had thickened the entire pyloric ring, and no metastases were visible as far as the abdominal incision permitted me to see. I favored the view that it was a hyperplastic gastritis. Yet at the autopsy it proved to be a scirrhus, for the fibrous, dense stroma contained a few narrow rows of cancer cells (cancer bodies) running parallel with the dense connective tissue. There was also a metastasis in the liver, larger and softer than the original tumor, and five small nodules in the omentum.

The proliferation of the great majority of cancers in the digestive tract starts from the surface, cylindrical, or columnar epithelium, or from the gland cells. Hanseemann asserts that carcinomata of the stomach occur, which cause death without having ever penetrated downward. This author also refers to the extensive carcinomatous destruction at the vaginal portion of the cervix, in which all the cancer cones are still connected with one another, and with the lower surface.<sup>1</sup> Twice I observed the same condition in the intestines, others report this state in the peptic ulcers and in canceroids of the œsophagus. It represents a growing down into the deeper layers while maintaining a real continuity with the surface, not only a microscopic continuity. These are real cancers without heterotopia of the cells. If a diagnosis is to be made in such a case we cannot start from the coarse, structural image, but we must view the morphological change in the cells themselves, if such change is at all discoverable. At this stage of affairs Hanseemann insists that we must investigate the anaplastic changes in cells if we want to attain a diagnosis at all in such cases.

To recognize the condition of anaplasia in tumor cells is not as easy a matter as Hanseemann would persuade us to believe. It was emphasized before, in this connection, that only the positive result is of any importance for the diagnosis, that the absence of certain characteristic appearances does not necessarily exclude cancer. To recognize anaplasia of cells we must bring in array all possible factors which may influence the process. It is especially necessary for this that the histogenesis of the tumor be determined or that this be reasoned out from its form and location. It is also necessary to know accurately from experience all the morphological, physiological, and especially the formative properties of the parent cells. Then the form of the tumor cells should be especially compared with those of the parent cells. Then we should try to form a conception of the life-history of the tumor cells, how they appear in their youthful condition, how they develop, if and how they finally die. This should also all be compared with the fate of the parent cell. Then we should try to

<sup>1</sup> Cullen. Carcinoma of the Uterus.

find out as much as possible about the functions of the cells, from the histological picture—whether the secretion is a normal one, an increased, weakened, or changed one. Furthermore, if they form an intercellular substance, and if this corresponds to the normal one of the parent tissue, that is, fibrous, osseous, or cartilaginous, lumpy or otherwise.

Finally, we come to the nucleus—segmentation figures—the karyokinesis or mitosis. As to the pathological forms more directly, I may repeat that the simple occurrence of hyperchromatic, abortive, or other pathological mitoses is of no importance at all for the diagnosis. If, however, such pathological mitoses are abundant and considerably heaped together, we can assume with tolerable certainty that a malignant tumor exists. This is not a physiological necessity, but a matter of experience, that a larger collection of pathological mitoses (nucleus-segmentation figures) occurs only with malignant tumors. It would, therefore, be theoretically possible that this should occur also in cases of benign tumors, but Hansemann claims to have never observed it. The presence of atypic mitoses in benign tumors is reported by Lubarsch (loc. cit.), and undeniably does occur, but it is the exception, not the rule. In all benign tumors, however, the pathological mitoses are few and isolated. Of course, there are malignant tumors in which very few pathological mitoses are found. The number of the mitoses is of no importance whatsoever for the kind of the tumor, and it would be entirely erroneous to desire to conclude from a collection of mitoses at all that the proliferation is malignant. In reality it denotes a rapid increase in the cells, and is everywhere found where tissue grows rapidly or is rapidly degenerated. A small number of mitoses are also sometimes seen in malignant tumors if a momentary stoppage of the growth has taken place.

The most important diagnostic factor of the mitoses has always been the variation from the normal forms of the mother-tissue. If such differences are found, it is a sure sign of anaplasia. To avoid every misunderstanding, however, Hansemann repeats that it is not the question of one figure or of another, but that a change must have taken place in the physiological mitoses throughout if one wants to decide upon an anaplasia. Only the positive result is of value, the negative has no value whatsoever.

All observations of mitoses have reliable value only when made on faultless material. In specimens obtained by washing the stomach, post-mortem changes frequently make this part of the examination impossible, since the nuclear forms change very easily, and also because their number decreases. But by my method of gastric curettage with a stomach-tube (see Hemmeter, *Diseases of the Stomach*, third edition) specimens may be obtained in a fresh condition, showing in some cases



of gastric carcinoma an abundance of abnormal mitoses. At times, however, and more frequently than generally supposed, pieces showing the actual structure of carcinoma are thus gained.

In many cases the determination of the regressive metamorphoses in the parenchyma may be of importance. All malignant tumors show an especial tendency toward disintegration, and especially cancers, which are situated on the surface, almost always form ulcers. But it must be remembered that such a metamorphosis also occurs in benign tumors, for instance, in myomas, and that the syphilitic tumors undergo an excessive fat metamorphosis accompanied by caseation. This property of malignant tumors is only to be utilized for the diagnosis in connection with the entire structure, and in itself is not conclusive. Only in those cases in which it presents a form which is not peculiar to the parent cells under other conditions does it point to the anaplastic changes of the cells.

Accordingly, Hanseemann emphasizes that it is possible to diagnose malignancy from the parenchyma of tumors alone. This is not true for all cases, but for many. Practically there is little opportunity or necessity to make use of studies of anaplasia for the diagnosis of neoplasms of the digestive tract. Moreover, the importance of these changes as diagnostic and pathogenetic factors has been lessened by the critical logic of Lubarsch (*loc. cit.*), Ribbert (*loc. cit.*), and others. Specimens gained at operation or autopsy, as a rule, permit of a diagnosis, from the presence of heterotopia and metastases, in my experience. The stroma in itself, however, furnishes no argument for the diagnosis of malignancy, and only when it accompanies the parenchyma does it complete the histological picture from which was derived the definition of cancers and sarcomas. It must be repeated here again specially that the infiltration of the stroma does not form a basis for the diagnosis, since there are both cancers and benign neoplasms without such infiltration, and benign inflammatory proliferation with it. A number of times I have observed that in portions of adenocarcinoma of the stomach that were derived from the glandular layer the stroma was made up of connective tissue, but in pieces from the muscularis the stroma was composed entirely of muscle fibres. This shows that the stroma may vary, according to the heterotopia.

Cancers of the mouth, œsophagus, stomach, intestines, and rectum, therefore, are diagnosed: 1. According to their structure. 2. Their topographical conduct toward neighboring tissues. 3. According to the properties of the parenchyma in comparison with the parent tissue.

On the other hand, the concept of sarcoma is somewhat more arbitrary. There are some, to be sure, which we recognize in the same way as cancers are recognized. These are the neoplasms presenting a specificity in the structure of their parenchyma—the chondrosarcomas,



osteosarcomas, myogliosarcomas, and lymphsarcomas. The others, however, are characterized by their structure alone, by the development of their cells and the formation of an intercellular substance. In four cases I encountered sarcomata of the intestines with indifferent spindle or round cells, the comparison of which with the parent cells was impossible; malignancy had to be determined by the topography of the same, that is, from the heterotopic development of the tumor. The advance of the tumor into neighboring tissues is what gives the decision alone, for the diagnosis of malignancy. The more the tumor is developed, the easier the diagnosis. But just at the first stages, when a decision would be most valuable, the characteristic criteria very often are lacking, and we must content ourselves with a probable diagnosis. M. Borst suggests that it will always be better in such cases to make the prognosis worse rather than better. This statement cannot well be harmonized with that of Virchow, that there are neoplasms of such perplexing structures that they may be designated as sarcomas or something else, just as the observer pleases.

While we can yet form diagnoses, with tolerable certainty, of the two forms of tumors, cancers, and sarcomas, the malignancy of complex tumors is exceedingly uncertain, and only to be diagnosed from the anatomical picture when its malignancy has already become manifest, that is, when real metastases have been developed. It is well known that all these tumors have occasionally become malignant. Why, however, they should at one time remain confined to their primary position, at another go beyond it and form metastases, is entirely beyond our discernment. No such judgment is possible from the histological structure. However, mixed tumors of the kidneys and uterus are always malignant, and such tumors in some other organs always become malignant if they exist for some time. To this class belong the papillary cysts of the kidneys and ovaries, besides the tumors growing from parts in the neighborhood of the kidneys to the kidneys themselves, which finally spread to the vena cava and form metastases throughout the body.

One of the most striking phenomena of all malignant tumors is the very widely differing degree of their malignancy, which fact has been mentioned several times. There are even cancers which exist ten years or more without revealing their malignancy in the shape of metastases. The question may be asked, "Can any deductions be made from the histological structure concerning the degree of malignancy?" The study of anaplasia might furnish a starting point for this, for from it we see without a doubt that those cells which have most increased in the power of independent existence must also most easily give rise to the formation of metastases. Since this is expressed by the degree of variation from the parent tissue a certain parallelism

ought to exist between the degree of anaplasia and the degree of malignancy. In order to control this question, Hanseemann made the following two series of observations. At one time the metastases and recurrences were compared with the primary tumors, and it was seen that they showed the same or a greater degree of anaplasia than the primary tumors, never a less degree. Furthermore, tumors with very extended dissemination through the entire body show strong anaplasia; such with uncommon local extension, without dissemination, show slight anaplasia. There are few exceptions to this law. For theoretic consideration Hanseemann considered this law proved in general; the greater the anaplasia the greater the tendency to form metastases. The second series of observations was concerned with carrying this theory over into practice. For this purpose he made notes as to the degree of anaplasia and the consequently expected tendency to recurrences of metastases. These prognosticated data were, as far as possible, controlled and compared with the later real course of events. The result was as follows: If the tumor was found to be very anaplastic, recurrences and metastases were hardly ever lacking. If, however, the tumor was but slightly anaplastic, either no recurrence or metastases occurred, or they developed with greater or great anaplasia. It has not yet been discovered on what fact it depends that a tumor becomes more anaplastic, and, therefore, the prognosis in all such cases is doubtful. Here, also, strong anaplasia gives more information than anaplasia which is slight or not discoverable at all.

My personal experience, as far as the practical application of this theory to the relative frequency of recurrences or metastases in cases of gastro-intestinal neoplasms is concerned, is that in all of my cases of this sort recurrences were recorded in from one to three years after the operation. I mean in all cases, of course, the future history of which could be traced up; that is, in forty-eight out of sixty operated cases.

I included in this list only such cases at which no metastases were visible at the operation.

The factors necessary to constitute anaplasia are not readily comprehended or recognized. 1. The establishment of the histogenesis of the tumor from its form and localization. 2. An accurate knowledge of the morphological, physiological, and formative peculiarities of the mother cells. 3. Comparison of the forms of tumor cells with those of the mother cells. 4. The biology—*i. e.*, life history of the tumor cells—their youthful appearance, their growth, their decline and death. 5. Determination of the function of the tumor cells, whether they secrete or not. 6. Character of the intercellular substance and its comparison with that of the mother tissue. All of these factors demand much critical discernment, large casuistic experience,

and patient judgment, so much so that the study of anaplasia is practically impossible outside of pathological laboratories.

Before concluding I desire to call attention to the gastric adenoma originating on the basis of a gastric ulcer. It is a well-known fact of pathology that the human gastric or peptic ulcer may become transformed into an adenocarcinoma apparently spontaneously. This process has been described in a classical investigation by Hauser.<sup>1</sup>

In 1900 I paid a visit to Prof. Hauser's laboratory at the University of Erlangen, and was fortunate enough to see some of his original preparations and sections. I have also had a rather exceptional clinical experience with cases of gastric ulcer in the human being, which I had studied in one case for over two years, during which it presented the typical clinical history of gastric ulcer. Then followed the clinical history of gastric carcinoma and death.<sup>2</sup> Naturally the question arose in my mind: "If gastric ulcers could be produced experimentally in animals, their transmission into possible adenocarcinoma might be studied at will, or the transformation into adenocarcinoma might be attempted by the transplantation of malignant neoplasms derived from other animals of the same species, or by the injection of sterilized filtrate of ground-up adenocarcinoma of other animals of the same species into the tissues surrounding the edge of the ulcer."

Among the causes that are definitely ascertained as contributing to the bringing about of gastric ulcer are especially three:<sup>3</sup> 1. Impaired vitality or injury to the mucosa of the stomach. 2. Hyperacidity or super-secretion of gastric juice containing an excess of HCl and proteolytic ferments. 3. An altered state of the blood.

All three of these factors may be produced artificially, and when we do produce them in the laboratory on animals, peptic ulcers arise in such a large proportion of the animals thus experimented upon that we have a right to conclude that they are directly attributable to the method pursued. When I speak of peptic gastric ulcer I mean the typical "*Chronisches Magengeschwür*" as described by Hauser.<sup>4</sup> For defects can be produced in the dog's stomach, for instance (and the literature on the experimental production of gastric ulcer proves this conclusively), which are not true gastric ulcers, but simply ulcerating lesions which heal rapidly. Gustav Fütterer<sup>5</sup> has produced such lesions by applying to the stomach caustics, ligating the gastric arteries, cutting off the supply of nutrition by stitching large portions of the mucosa

<sup>1</sup> Das chronische Magengeschwür, sein Vernarbungs-Proceß und die Beziehung zur Entwicklung des Magenkrebses, Leipzig, 1883; and Das Cylinder-epithelkrebs des Magens und des Dickdarms, Jena, 1890. See also Hemmeter, New York Medical Record, 1897, vol. lli., p. 365. Also Hemmeter, Diseases of the Stomach, 3d ed., p. 560.

<sup>2</sup> Hemmeter. New York Medical Record, 1897, loc. cit.

<sup>3</sup> Hemmeter. Diseases of the Stomach, 3d ed., p. 491.

<sup>4</sup> Loc. cit.

<sup>5</sup> Ueber die Aetiologie des Carcinoms, p. 115.



with catgut sutures. Defects resulted, but they all healed in a short time. Even when one-third of the quantity of the animal's blood was withdrawn, such defects had healed in two weeks. In 1896 Silbermann produced gastric ulcers in dogs by either tying the gastric arteries or causing emboli in them by injecting suspensions of lead chromate. Thereafter he injected hæmoglobin and pyrogallie acid (acid pyrogallie 0.1 to 0.14 per cent.). When Fütterer resected the gastric mucosa, as stated before, and made injections of pyrogallie acid, he could confirm Silbermann's results and produced ulcers of the stomach which in every histological detail corresponded to the chronic gastric ulcer of the human being. By this method, employed by Fütterer and Silbermann, I was successful in producing experimentally gastric ulcers. In one series of experiments eleven dogs out of thirty operated upon developed typical gastric ulcers.<sup>1</sup>

Now I had a method by which this characteristic lesion could be produced experimentally. The next question was: "Could these lesions be in any way experimentally transformed into adenocarcinoma of the stomach, or would they become transformed into adenocarcinoma spontaneously, as has been definitely known to occur in the human being, and as Fütterer has observed, to occur in a rabbit in which he had artificially produced a gastric ulcer by the method described?"<sup>1</sup>

Hauser has described a structural characteristic of the adenocarcinoma of the stomach, which has developed on the basis of a gastric ulcer, and which is not observed in ulcerating carcinomas not developed on this basis. This characteristic, by which the so-called "ulcus-carcinomatousum" can be recognized, consists in a very peculiar behavior in the fibres of the chief muscular layer of the stomach, and also of the fibres of the muscularis mucosæ. This peculiar behavior of the muscularis consists in an oblique ascension of the fibres of the true muscular layer, and a descension of the fibres of the muscularis mucosa, the fibres of both muscular layers converging toward and fusing into each other in front of the edge of the ulcer, which is here composed mainly of connective tissue. The true muscularis bends upward in continuity, and the border of the ulcer, which is composed of very dense connective tissue, is limited by the lower surface of the turned-up true muscularis. Another feature of the *ulcus carcinomatousum* is that a section made perpendicular to the surface of the stomach, and through the entire bed of the ulcer, almost invariably exhibits the general outline of a fish-hook.<sup>3</sup>

For the causes which bring about this fish-hook formation (see Fütterer, loc. cit., p. 112), the main reason being that the lower edges of

<sup>1</sup> Hemmeter. Intracellular Catalytic Processes in Pathogenesis of Malignant Neoplasms. THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, April, 1903.

<sup>2</sup> Loc. cit., p. 152.

<sup>3</sup> Hemmeter's Diseases of the Stomach, 3d ed., Plate IX.



FIG. 3.



the ulcer, near the pylorus, are, during the efforts of the gastric peristalsis to evacuate the gastric chyme into the duodenum, exposed to the most mechanical irritation, and accordingly Fütterer has shown that adenocarcinoma, if it develops from an ulcer, always develops from the lower edge. This location for the development of gastric ulcer has already been emphasized in a publication by Dr. Delano Ames and myself,<sup>1</sup> but it is the desert of Fütterer to have emphasized this point as an etiological factor in the causation of *ulcus carcinomatosum*.

I should add that in repeating the experimental production of gastric ulcer according to the methods of Silbermann<sup>2</sup> and Fütterer,<sup>3</sup> I not only produced mechanical defects and injected pyrogallie acid in the method described, but I maintained a very high acidity for free HCl in the gastric chyme of the dog by supplying this acid in his food, and also pouring it into his stomach through a soft rubber tube. In February, 1900, I came into the possession of a mongrel fox-terrier that persistently vomited his food. The vomit contained no free HCl nor ferments, and at the autopsy a cancer of the stomach was found near the pylorus. Transplantations with this material were made into the stomach of other fox-terriers, but I was not successful in producing a gastric carcinoma in any of these other animals inoculated.<sup>4</sup> Dr. Leo Loeb has undoubtedly succeeded in transplanting a sarcoma from one rat thus affected to a large number of other rats of different age and sex.<sup>5</sup> In my previous publication<sup>6</sup> I stated that, as far as I knew, Loeb's work had not been confirmed. In a private communication Dr. Loeb informs me that Ehrlich and others confirmed his results. A sterile extract of part of this canine carcinoma was also made and preserved for inoculation and injections into the stomachs of dogs in which I

<sup>1</sup> New York Medical Record, September 11, 1897.

<sup>2</sup> *Loc. cit.*

<sup>3</sup> *Loc. cit.*

<sup>4</sup> Sepsis followed a large proportion of the operations, and I could not secure the aid of a competent surgeon who would do these operations aseptically for me.

<sup>5</sup> Journal of Medical Research, vol. vi. No. 1.

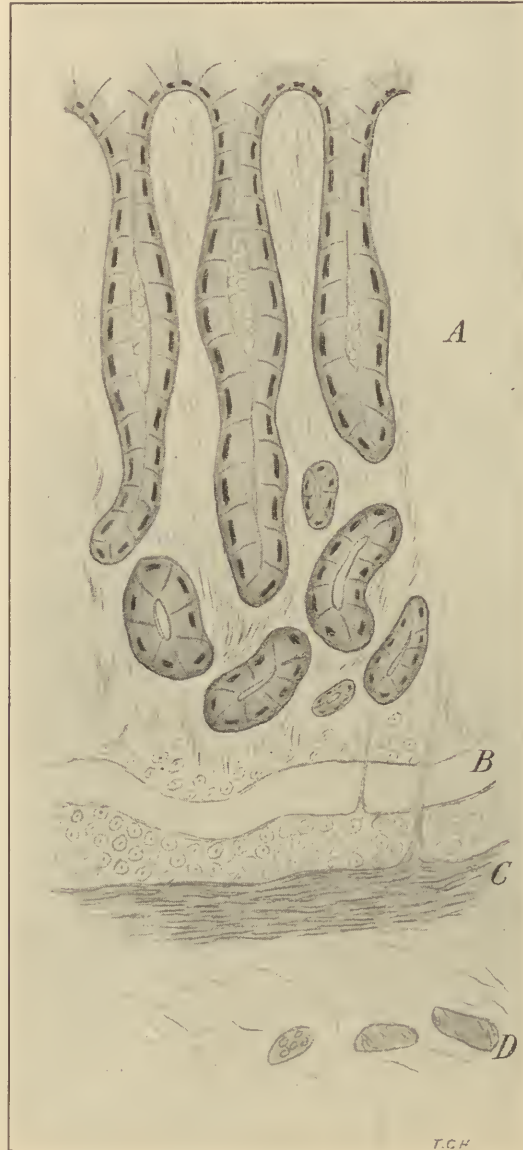
<sup>6</sup> THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, April, 1903.

FIG. 3.—*Ulcus carcinomatosum* of the pylorus. *A*. A section through the wall of the stomach, showing the edge and a portion of the base of the ulcer. Objective, two-thirds; eye-piece, two inches. Stained with hematoxylin and eosin. The drawing is built up from a series of microscopic fields.  $\times$  about 15 diameters. *d*. Mucous membrane. *m*. Muscularis mucosæ. *s*. Submucosa. *a*. Base of the ulcer. *mm*. Muscle coat of the stomach. *mc*. Groups of cancer cells between the bundles of muscle fibres. *dc*. Groups of cancer cells in the edge of the ulcer in the mucous membrane. *sc*. Groups of cancer cells in the submucosæ. *a*. Necrotic membrane lining the base of the ulcer.

*B*. A small nodule from the serous coat of the stomach over the base of the ulcer. Objective, two-thirds; eye-piece, two inches. Stained with hematoxylin and eosin.  $\times$  about 15 diameters. This figure gives a good idea of one of the nodules in the serosa. It is composed entirely of a collection of groups and masses of cancer cells so closely packed that the outlines of the individual cells cannot be made out. Except for these nodular thickenings, the serosa was not altered. *pc*. Cancer masses in peritoneal coat.

expected to cause gastric ulcers. A very small quantity of filtrate (148 c.c.) was thus saved, as the largest part of the tumor had been used for transplantations.

FIG. 4.

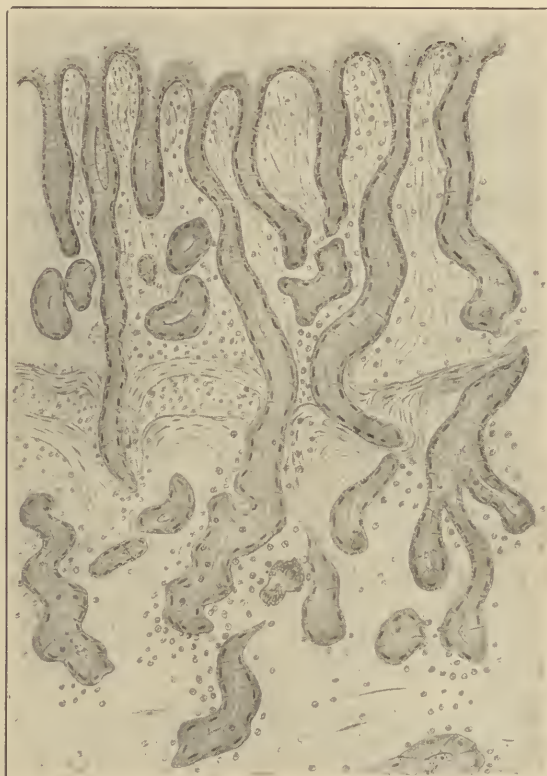


Normal gastric mucosa of dog. A. Glandular layer. B. A homogeneous layer characteristic of canine and feline stomachs. C. Muscularis mucosæ. D. Submucosa with few muscle bundles.



In the meanwhile the publications of Fütterer<sup>1</sup> appeared, and it occurred to me that possibly my failure to successfully transplant canine carcinoma was due to the fact that the stomach of the animal into which the inoculation was made was not in a susceptible condition, and that it must be transformed into such a condition by a

FIG. 5.



Adenomatous proliferation at edges of experimental gastric ulcer caused by injection of sterile and cell-free extract of gastric adenocarcinoma of a dog. *A.* Surface of gastric mucosa. *B.* Peptic gland ducts. *C.* Muscularis mucosae. *D.* Proliferating gland ducts that have broken through the muscularis mucosae. *E.* Gland cells in submucosa.

previous injury. This previous detriment to the tissue, in order to secure successful transplantation of the tumor, in the case of rats, has not been found necessary by Leo Loeb<sup>2</sup> and Herzog.<sup>3</sup> I did not succeed in securing another dog affected with carcinoma of the stomach

<sup>1</sup> Loc. cit.

<sup>2</sup> Journal of Medical Research, vol. viii, p. 44.

<sup>3</sup> Ibid., p. 74.



until after I had read Fütterer's work in 1901, and this second dog presented an adenocarcinoma which developed spontaneously at the edges of an experimental gastric ulcer. It presented the behavior of the two layers of the gastric muscularis as first described by Hauser, had a distinct fish-hook form, and exhibited heterotopia of gastric glands as first described by Virchow<sup>1</sup> and Hansemann.<sup>2</sup> This gastric cancer reached the size of a walnut, and two metastases were found in the peritoneum.

The practical deduction for the histological diagnosis for malignant tumors which can be made from the studies of Hauser, Fütterer and myself, is that it is possible to diagnose a carcinomatous ulcer of the stomach histologically by the characteristic behavior of the true muscularis and muscularis mucosæ, and by the form of a fish-hook presented in outline in a section through the edge of the ulcer nearest the pylorus. By these striking features I believe we are justified in concluding that any gastric adenocarcinoma presenting them has been developed on the basis of a pre-existing gastric ulcer.

In the April number of this JOURNAL I have reported the results of my experiment attempting the transformation of experimental gastric ulcer into adenocarcinoma by injecting the extract of a canine gastric carcinoma into the edges of the ulcer. Very striking adenomatous proliferations can be produced in this way, but they cannot be called carcinomas. I include here the photographs of some of the sections, showing these experimental adenomas.

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<sup>1</sup> His' *Archiv*, Bd. iii.

<sup>2</sup> *Loc. cit.*, p. 195.



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## THE INFLUENCE OF THE UNIVERSITY OF MARY- LAND ON MEDICAL EDUCATION.<sup>1</sup>

BY

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SYNOPSIS:—DIFFERENCES BETWEEN "FACTS" AND "TRUTHS":  
DISCONNECTED FACTS HAVE NO SIGNIFICANCE UNTIL THEY  
BECOME PART OF THE SYNTHETIC STRUCTURE OF A SCIENCE:  
EXTRACTS FROM THE HISTORY OF THE UNIVERSITY OF MARY-  
LAND, SHOWING ITS INFLUENCE ON MEDICAL EDUCATION:  
MODERN PHYSIOLOGIC DISCIPLINE: METHODS OF MEDICAL  
TRAINING: THE LECTURE, THE LABORATORY, TEXTBOOKS, CON-  
FERENCES: VALUE OF INSPIRATION COMING FROM MEDICAL  
WORK.

Today we begin the study of one of the most important  
and beautiful sciences which the human intellect has system-  
atized.

Alexander von Humboldt, in his monumental work, "*Kosmos*," describes in a very beautiful manner the condition of the mind in one to whom a promised land of research of any kind has opened itself. The following are his words: "It is a custom of those who would like to conduct others to the summit of mountains, to describe the path as pleasanter and easier than it will be found in reality. It is their habit to praise the glorious views from the mountains, even though they may divine that large portions of the regions below may be concealed in fog. They know also that in this concealment there is a mysterious charm, and that a hazy perspective distance produces the impression of infinity, reflecting in a serious and divining manner in the mind and in the sentiments." (*Kosmos*.) I may add that this feeling of mysterious charm will in the right kind of mind elicit the desire of a closer acquaintance with that region seemingly so far away; and this is about the conception that I have of the sentiments with which an investigator should approach the solution of difficult problems of any kind. The charm and the stimulation which come from everything that

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<sup>1</sup> Address at the beginning of the course on Physiology at the University of Maryland, October 1, 1903.



is new and not understood, make us put up with many a stony path and much hard work. In connection with the accumulation of facts of experience and experiment in medicine, the correlation of which with our general knowledge of already established truths has not yet taken place, Humboldt says: "It is a safe criterion of the quantity and quality of the discoveries which we may expect in any science, when the facts seem yet to stand isolated and without relation to one another." The great plethora of experimental results, therefore, is rather to be interpreted as a good sign, only we will have to be cautious not to regard in the light of a *law* what is in reality only a recent acquisition, standing, as a rule, in very loose relation or having no connection at all, with the synthetic structure of physiologic knowledge.

We are living in a period in the history of medicine in which the experimental tendency has gained supremacy over speculative philosophy in medicine. But we are in the possession of such an enormous amount of new material and facts, which by additional experiments is daily increasing, that the new facts frequently must be allowed to remain unused, and are, for the time being, of no assistance in the advancement of our science. In this connection, I must again repeat what I have emphasized in the preface of the second volume of my work on "Diseases of the Intestines," namely, the difference between *truth* and mere *facts*. These two are often, unfortunately, considered synonymous. Facts are little truths that our senses are capable for the present of comprehending; but back of, and beyond these facts, later experience often reveals the higher and greater truth. An experimental fact which today seems absolutely disconnected and therefore without meaning, may tomorrow, when viewed in another light, suddenly assume a far-reaching significance and importance. No new fact of experience or experiment, be it at present apparently ever so remote from practical bearing, need be considered worthless, provided it is correct. It may be allowed to rest as raw material for a time, but it is probable that in another association it may acquire an importance which we did not anticipate.

But this I must emphasize that an isolated, disconnected fact of experience or experiment, has for the time being no significance for the progress of medicine. This significance comes only then when we can arrange and fix this fact into the already existing and firmly established architecture of our knowledge. There exists a danger in over-rating the value of single facts of experience and experiment. Individual facts discovered this way are accumulating to such an extent that we are completely submerged under an ocean of experimental results, and the intellectual interpretation which fits them into

the synthetic structure of our science is missing. Physicians who are not participants in experimental undertakings, feel this absence of the connecting link between an enormous number of new acquisitions very painfully, which though experimental are in a sense empiric. This is also true of the experimental acquisitions in bacteriologic as well as biochemic domains. In the eighteenth and during the first part of the nineteenth centuries medicine was comparable to a sterile unproductive heath, in which some evil spirits drove about the speculating medical philosophers in a circle. Now we have got into an over-fruitful swamp or jungle in which the facts grow so luxuriantly that they threaten to smother our thinking powers. The tendency of all laboratories is to bring out new facts. Let us have all of them if it must be, but what we need as much, if not more than new facts, are master minds who will instruct us in the interpretation of these and old facts, and give them a meaning and value by fitting them into the synthetic structure of physiology and medicine. Martius<sup>1</sup> compares modern medicine to a sense-confusing concert, and what is needed is a disciplinarian to instruct us concerning the leading motives, to seek the familiar law in the revealed wonders of the present time.

“Sucht das vertraute Gesetz in des Zufalls grausenden Wundern,  
Sucht den ruhenden Pol in der Erscheinungen Flucht.”  
(SCHILLER.)

If these halls could speak they could inform you of nearly a century of medical teaching that would constitute a most interesting part of the history of American medicine. If this dome could repeat the words that have been spoken under its sky-lit arch, it would tell you of teachers who, through their erudition, theoretic and practical training, broad experience and critical judgment, ranked among the masters of medicine. If those benches upon which you are sitting could tell their story they would inform you of generations of truth-seeking students who have occupied them, coming not only from all parts of this great country, but from other countries the world over. If, as Churchill says, greatness is a combination in the same individual of unusual moral and unusual intellectual force, then we have had many great teachers in this institution. What constitutes the greatness of teachers, and what constitutes and indicates the greatness of a university? Certainly not the bricks and mortar of which the buildings are constructed, nor even the rich endow-

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<sup>1</sup> Pathogenese Innerer Krankheiten.

ments, but the men it has produced. And what constitutes a great medical man? The general acceptance that the work which he has done is exceptionally useful and has left a permanent record in the annals of the science in which he was active. The principle exponents of merit in medical men are the following: (1) That they have accomplished research work involving new and valuable discoveries, useful in the art and science of medicine; (2) that they occupy positions of recognized importance in the medical profession, either as teachers, investigators, editors of high-class medical journals, high positions in the medical service of the army and navy; (3) that they are authors of medical works of recognized merit by which our knowledge of the normal and abnormal functioning of the human body has been advanced. If we apply these tests to the alumni of the University of Maryland we will find that we can be justly proud of the record of our school. For not only have we among them research workers who have made valuable contributions to the art and science of medicine, beginning with the contributions of Professor Charles Frick and Nathan R. Smith in the art of surgery, and extending to the discovery of the microorganism which is the cause of smallpox, discovered during the present year by our alumnus, William T. Councilman, at present professor of pathology in Harvard University, Boston, but we have had a large number of our alumni to fill positions of prominence in the profession throughout the country. Professor E. F. Cordell, who this year fills the newly appointed chair of history of medicine in the University of Maryland, assures me that 8 or 10 of our alumni have been Surgeon-Generals of the U. S. Army or Navy. Quite a number of our alumni still living are professors in standard medical institutions of the country. In this city there is not a medical school which has not several alumni of the University of Maryland on its teaching staff, and of medical institutions outside of Baltimore, I need only mention the names of Alexander C. Abbott, professor of hygiene and bacteriology in the University of Pennsylvania; Charles P. Noble, surgeon-in-chief to the Kensington Hospital of Philadelphia; Roberts Bartholow, emeritus professor of materia medica and therapeutics, Jefferson Medical College, Philadelphia; William T. Howard, Jr., professor of pathology at the Western Reserve University in Cleveland, O.; John W. Williams, professor of obstetrics, Johns Hopkins University; Professor William T. Councilman, of Harvard University, Boston. In addition to these, who are full professors, a large number of associate professors and instructors in other institutions could be mentioned.

I can only refer in a passing manner to the medical works written by alumni of this university. The books of Charles

Frick, Nathan R. Smith, Robley Dunglison,<sup>1</sup> Roberts Bartholow, Alexander Abbott, John W. Williams, Henry Berkeley, the writings on the history of medicine by Eugene F. Cordell, the contributions to pathology by W. T. Howard, Jr., and William T. Councilman, William Alexander Hammond,<sup>2</sup> Professor of Physiology in the University of Maryland, 1860, and Surgeon-General United States Army, 1862, and the works of members of the faculty still active on our staff. In enumerating the literary contributions of our alumni I should have mentioned the writings of William Canfield and his work on Urinary Analysis, written while he was the editor of the *Maryland Medical Journal*. And no doubt numerous other highly valuable contributions have escaped my memory. Eight works of acknowledged merit have been published by present members of our medical faculty and two more are in preparation. But enough has been mentioned to convince you of the honorable history of this institution which you have entered, and of the priceless heritage which it is our duty to uphold and to enlarge upon in future.

We have it on very good authority, that of James Russell Lowell, that when one is to make an address, he can begin by doing one of 3 things: (1) Narrate an anecdote; (2) make a quotation; or (3) express a sentiment. There will be abundant opportunity to avail myself of this advice in our future communications, but the sentiment that I should like to express at present is that we can derive an abundance of inspiration and encouragement from the interesting history of this school, and that we can apply to the records thereof the sentiment expressed in the words of Longfellow:

“Lives of great men all remind us  
We can make our lives sublime,  
And, departing, leave behind us  
Footprints on the sands of time.”

And now what shall I say concerning the life and work of that lovable physician, scientist, and gentleman in whose footsteps I have the honor to follow today? The attempt to give due credit to the character and genius of Professor Francis T. Miles would lead me to falter in the effort to eulogize his work,

<sup>1</sup> According to Allibone (see Cordell's History of the University of Maryland, p. 77), the sale of Dunglison's principal works in 1858 amounted to 100,000 volumes. He was the founder of the medical faculty of the University of Virginia. Graduate of University of Erlangen, 1829. In 1836 professor of Institute Medicine, Jefferson Medical College, Philadelphia.

<sup>2</sup> William A. Hammond, professor of physiology, University of Maryland, 1860, originated the Army Medical Museum, and Medical Library, at Washington. His work on Diseases of the Nervous System (1871) went through 10 editions in 7 years.



to falter at the idea of the potency and inspiration which the example of his life has given us. My position as eulogizer in this case reminds me of a story of Sidney Smith. When he saw his grandchild patting the back of a huge sea-turtle, he said: "My dear, why are you doing that?" The child answered, "Grandfather, I did it to please the turtle." Thereupon Sidney Smith replied, "You might as well pat the dome of St. Paul's cathedral with a view to pleasing the dean and the chapter." And so I must confess my inability to add to the beauty of the life of F. T. Miles. His life, history, and work, narrated in the simplest tones, would constitute their own glorification. For who can picture to himself that sweet, gentle face, that venerable white beard, those thoughtful yet searching eyes, that wonderful command of language and control of diction, with which he could hold his audience spellbound, not only by the weight and intrinsic merit of the facts which he announced, but by the beautiful style in which he announced them. Who can recall him in the clinic as a diagnostician and therapist without unhesitatingly confessing that here we had before us the embodiment, the type of an American physician and scientific thinker.

When I entered this hall a few minutes ago it was with the silent prayer that I might merit the record which Miles has left behind him, that I might to a degree fill his chair, and display some of the grace and heart-winning interest which was habitual in him, and that when my time came to resign it to my successor, I might leave it with the same consciousness of having fulfilled my scientific and professional duty, and merit, as he has merited, the commendation "Well done, thou good and faithful servant; thou hast been faithful over a few things, I will make thee ruler over many things. Enter thou into the joy of thy Lord." (Matthew xxv, 21.)

To those of you who recently have entered these halls for the first time let me extend a cordial welcome. I know the doubts and apprehensions of the young medical disciple. Not so very many years ago I sat on these very benches myself, and remember distinctly and with grateful heart the words of encouragement and good cheer of my teachers. I wish I had a hundred hands, to extend them to each one of you individually, and to assure you, "Be not discouraged at the difficulties that you will encounter, but work and despair not." Cling to the inspiration which the history of the art and science of medicine offers, and develop this inspiration into an enthusiasm for work. For there can be no more inspiring and glorious history than that of medicine since it has become a science. I do not refer to the history of medicine prior to the establishment of universities, although even the medicine of the aborigines presents

much that is impressive. But I refer more particularly to the history of medicine as developed in the evolution of the civilized nations.

All ages have in their turn woven the laurel wreath for the brow of the physician. The verse of Homer, "A wise physician, skilled our wounds to heal is more than armies to the public weal," and the lines of Cicero, "There is nothing in which men so approach the gods as when they give health to other men," are among the early tributes to our profession. Charles IX proclaimed that all Protestants in France should be put to death on St. Bartholomew's day, but there was one single exception—Ambroise Paré, the father of French surgery. The honor of medicine is yours, its heroes are your heroes. The battlefield of the American revolution welcomed Drs. Mercer, Warren, and Rush. When the French army was entirely demoralized, Larry, the surgeon-general, inoculated himself with the plague to show that it was not contagious—their courage rose and they went on to victory. Think and rejoice at the progress from the time when ancient Hippocrates tried to cure the gastralgia of the great Pericles with hellebore and flaxseed poultices. Even since the time when Haller announced his theory of respiration, and Harvey explained the circulation of the blood, and Aselli taught the existence and uses of lymph-vessels; and the great Jenner balked the worst disease that scourged Europe, and Sydenham developed the normal recuperative forces of the physical organism, and cinchona bark stopped the shivering aches of the world. And Sir Astley Cooper, Abernethy, Hosack, Romeyn, Griscom, and Valentine Mott fought back death with their keen scalpels. What an ancestry—what a heritage. Think of Jenner—400,000 deaths annually in Germany, Great Britain, and Russia—he found that inoculation with virus from a cow that had gone through proper infection, arrested the scourge and saved more lives in a year than all the battles of a century destroyed. He was assailed by literary critics, the press, potentates, ministers. Small wits caricatured Jenner as riding in a procession of fools on the back of a great cow. Grave men expressed their opinions that all the degrading diseases of brute creation would be transplanted into the human family, and that horns would grow out of the foreheads of vaccinated persons, and they would begin to chew the cud. But his blessed discovery survived all prejudice; he is today recognized as one of the greatest benefactors of the human race.

And now to turn to that science which shall interest us for the coming year. Physiology is a comparatively recent department of human knowledge. Its historic development naturally depended upon that of anatomy. A people who had not cultivated the science of anatomy could of necessity know nothing of

physiology, and this dependence is evident at the present day. A knowledge of structure is indispensable to a knowledge of function. Physiology is the science of the regular processes that occur in living things, in plants and animals; and as the human being is an animal, the processes that occur in the different organs and systems of the human anatomy can be to a large extent studied by investigations on other animals, and all physiology does not apply exclusively to the human being, but to a certain extent to all animals. The understanding of the phenomena of life, which have been ascertained in living things, have been gained by 2 methods: One is called the method of observation, the other the method of experiment. Direct observation can only instruct us concerning a small portion of the phenomena of life, by far the greater part of these take place in the interior of the organism, and these can only be made accessible to observation by interferences into the normal processes of life, that is, generally by opening the body cavities or by isolating and removing organs and tissues. Every observation that is made under conditions artificially induced, constitutes an experiment. The art of experimentation has been admirably developed in the last 25 years, and has gradually necessitated the teaching of physiology by 2 methods, one by the so-called *didactic* method, in which the instruction is, as a rule, carried on in form of lectures or other personal communication between teacher and student, and the second is the *objective* or *laboratory* method, by which the student is made to understand the problems of physiology by demonstrations and experiments conducted in the laboratory. To begin with, the objective or laboratory method, I may say with Dr. William H. Welch, that "laboratory methods are extremely time-robbing and not adapted to teach the whole contents of any of the medical sciences. It is, of course, hopeless to attempt to demonstrate practically all of even the more important facts of physiology to the medical student." During the present year the University of Maryland will open to its students a new laboratory of physiology, in which they will be made familiar with the technic of experimentations and the fundamental principles of functioning of various tissues and organs will be *objectively* demonstrated. Concerning the didactic teaching, I will say that it will consist of lectures and conferences or examinations. We shall probably have 2 lectures and 1 conference weekly, in addition to the laboratory work.

The science of physiology has grown to enormous proportions. There are any number of textbooks of physiology in the various languages, every civilized nation has now its journals devoted exclusively to this science. In America we have the *American Journal of Physiology*, edited in 2 volumes

of 500 pages each, every year. In Germany in addition to a number of special journals devoted to physiology and physiologic chemistry there is a publication "Die Ergebnisse der Physiologie" (The Achievements and the Progress of Physiology) which comes out annually in 2 very large volumes (925 pages) representing in condensed abstracts and in larger connected essays the physiologic advances made in the preceding year. A similar work is the "Zeitschrift für Physiologie," edited by Professor Max Verworn. Indeed I may express about physiology what Huxley said in an essay on medical education in 1870, when he announced that "He had a very strong conviction that any one who adds to medical education one iota or one tittle beyond what is absolutely necessary is guilty of a very grave offense." In the same essay Huxley expresses himself as follows: "*What the student wants in a professor is a man who can stand between him and the infinite diversity and variety of human knowledge, and who shall gather all that together and abstract from it that which is capable of being assimilated by the mind.*"

In a discussion of the relative advantages of the instruction gained in the laboratory, and that gained by lectures and textbooks, we must bear in mind that medical education has a twofold object. To use the language of President Eliot, of Harvard University, the student must be "*trained for power,*" that means, first, he must be trained to *observe* carefully, *reason* correctly, *judge* wisely, and *study* effectively. (Bowditch, "Medical Education of the Future.") In the second place, he must be led to acquire a sufficiently large part of the medical knowledge of the time to make him a safe custodian of the health of the community. *Now it must be evident that "training for power" cannot be considered an essential function of a school of "applied" medicine, in which the aim of instruction is to impart direct and valuable information, where the object of all teaching is to give the greatest possible amount of useful knowledge.*

For the purpose of teaching students how to observe, to reason, to judge, and how to study, the laboratory is preferable to the didactic method. There can be no doubt that personal contact with the phenomena themselves, and not with descriptions of them is a powerful mental stimulant for the student; but we are by no means justified in concluding that the didactic methods, the lecture, the textbook, and the recitation are worthless as methods of medical training.

The pendulum of reform has occasionally made extreme excursions in the history of medical education.

Whenever a given method has been found to give unsatisfactory results, there is a strong tendency to abandon it alto-



gether in favor of some entirely different and, as a rule, not much tried method. Dr. Burr in 1899 characterizes the didactic lecture as an "anachronism," dating from the time when printing was unknown and manuscripts were rare and priceless and the only means of communicating knowledge was by "word of mouth."<sup>1</sup> In *Science* for July 7, 1899, Professor C. S. Minot expresses himself similarly: "The very best that can be said of a lecture or a book," he writes, "is that it describes well the knowledge which some one possesses." He goes so far as to assert: "There is no knowledge in books.(!) Knowledge lives in the laboratory; when it is dead we bury it decently in books. . . . A lecture is a spoken book." To this Professor Bowditch<sup>2</sup> caustically remarks: "I venture to believe that Professor Minot's students will hardly agree with this estimate of the lifeless character of either his written or his spoken instruction."

In their efforts to substitute objective or laboratory training for didactic or lecture teaching, the reformers have, in my opinion, gone to extremes. As Professor W. H. Howell, has expressed it: "These gentlemen, having become possessed of the golden truth that the best knowledge is that which comes from personal experience, seem disposed to deny all value to knowledge communicated from the experience of others."<sup>3</sup> As a matter of fact, there are territories of necessary medical training in which the laboratory cannot possibly replace the lecture, and it is quite as possible to abuse the laboratory as it is to abuse the didactic method of instruction, and as Bowditch<sup>4</sup> says: "In all schemes of education a *good* teacher with a *bad* method is more effective than a *bad* teacher with a *good* method."

This distinguished American physiologist has emphasized that in physiology, as in other departments of medicine, we have to deal with subjects which lie within what Michael Foster has called the "penumbra" of solid scientific acquisition and about which conflicting views are unavoidable. Here the experienced lecturer has the best opportunity to train the judgment of his pupils by illuminating first one and then the other evidence upon which the opposing views rest temporarily. Other facts and principles which can not properly be made the subject of laboratory instruction, are the historic presentation of subjects, for few things are more instructive than to follow up step by step the lines along which our knowledge has advanced.

<sup>1</sup> Philadelphia Medical Journal, October 21, 1899.

<sup>2</sup> "The Medical School of the Future," Trans. Congress of American Physicians and Surgeons, Vol. v, 1900.

<sup>3</sup> The Michigan Alumnus, January, 1900, Vol. vi, p. 143.

<sup>4</sup> L. c., p. 115.

Then, again, equally competent observers differ in their conception of well-observed phenomena in physiology, and it at times becomes necessary to point out to the student, the most probable way of reconciling conflicting observations. Such doubtful territories offer highly beneficial opportunities for mental training, but here the conference or recitation is better suited than the lecture, for in the conference the minds of the teacher and pupil are brought most closely in contact, the student's difficulties are appreciated by the instructor and the point of view of the teacher can be understood by the student. To quote Professor Bowditch once more<sup>1</sup> "no higher enjoyment falls to the lot of the teacher than that which he experiences when by a series of carefully considered questions he leads his pupil onward from the known to the unknown, and notes the gleam of intelligence which illumines his countenance as a subject previously obscure becomes clear as a result of his own mental operations guided by his teacher's skillful questions."

No monopoly of opportunities for mental training can be claimed—either for the laboratory, the lecture, or the recitation—they must all be used, and each in its proper sphere of usefulness.

All knowledge and study should have a value to us beyond its practical one, and that value lies in the ennobling, elevating, and edifying influence which all acquisition of higher truth exerts—I mean the cultural value of knowledge. The starry heavens had to Immanuel Kant a value beyond their astro-nomic one. The setting sun, as it mantled with bloom of roses, the Alpine snows had a value to John Tyndall beyond its optical one. . . . The sound of a village bell, as it came mellowed from the valley to the traveler on the hill had a value to Helmholtz beyond its acoustic one. To the great botanist Linné the lilies of the valley had a value beyond their botanic one. A certain lightening of the heart, he said, accompanied the declaration "*that Solomon in all his glory was not arrayed like one of these.*" And so let our physiologic studies have a value beyond their practical bearing on medicine.

Do you want to know how to make the study of physiology easy? Why learn to love physiologic work; do not let your study become a drudgery—or irksome.

Sir Andrew Clark once delivered an impressive "lay sermon" on the ways to acquire the "love of work," and this great clinician was also a thorough student of human nature. In the address I refer to, he said:

Firstly I believe that every man's success is within him-

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<sup>1</sup> L. c., p. 113.

self, and must come out of himself. No true, abiding and just success can come to any man in any other way. Secondly, a man must be seriously in earnest. He must act with singleness of heart and purpose; he must do with all his might and with all his concentration of thought the one thing at the one time which he is called upon to do. And if some of my young friends should say here "I cannot do that—I cannot love work," then I answer that there is a certain remedy, and it is work. Work in spite of yourself, and make the habit of work, and when the habit of work is formed it will be transfigured into the love of work; and at last you will not only abhor idleness, but you will have no happiness out of the work which then you are constrained from love to do. Thirdly, the man must be charitable, not censorious—self-effacing, not self-seeking; and he must try at once to think and do the best for his rivals and antagonists that can be done. Fourthly, the man must believe that labor is life, that successful labor is life and gladness, and that successful labor with high aims and just objects, will bring to him the fullest, truest, and happiest life that can be lived upon the earth.

Let me but do my work from day to day,  
 In field or forest, at the desk or loom,  
 In roaring market place, or tranquil room;  
 Let me but find it in my heart to say,  
 When vagrant wishes beckon me astray,  
 "This is my work; my blessing not my doom;  
 Of all who live I am the one by whom  
 This work can best be done in the right way."

Then shall I see it not too great nor small  
 To suit my spirit, and to prove my powers;  
 Then shall I cheerful greet the laboring hours;  
 And cheerful turn when the long shadows fall  
 At eventide, to play and love and rest  
 Because I know for me my work is best.

(VAN DYKE.)

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[Reprinted from *American Medicine*, Vol. VI, No. 20, pages 777-781,  
November 14, 1903.]

## CHRONIC MALARIA: COMPLICATIONS AND SE- QUELÆ WITH SPECIAL REFERENCE TO DIGES- TIVE COMPLICATIONS.\*

BY

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*History.*—Historic records of the human race give the undoubted evidence that malaria is one of its oldest enemies. During the migrations and wars of antique nations the poisonous emanations of swamps are described as having claimed countless victims. Unmistakable descriptions of some forms of malaria are found in the writings of Protagoras, 500 B. C. The disease was well known to later Greek and Roman physicians (Celsus and Archigenes). It is probable that the drainage and sewage system recently discovered among the hills of Rome, and to which a great antiquity is ascribed, was constructed with the conscious purpose of ridding the soil of the endemic malarial fever. In Arabic medicine the various forms of malaria and their causative relationship are well described.

Agriculture and malaria are two factors which mutually control each other in the early history of the human race. Where there was no culture of the ground, malaria was exuberant, and the disease declined as soon as the ground was cultivated. There is no distinct reference to malaria in the papyrus of Ebers; but according to W. Groff, malaria was well known to the ancient Egyptians. The word "*Aat*," which occurs in the inscriptions on the temple of Denderah, refers to the annual recurrence of chills and fever. The entire history of our knowledge of malaria can be divided into 3 epochs: (1) The antique history, descending to the time of the discovery of the specific virtues of cinchona bark; (2) the period between this discovery (about 1640) and the discovery of the malaria parasite by Laveran (1880); (3) the development of malarial hygiene, prophylaxis and parasitology since 1880. The most important and far-reaching of these events was the

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\* Address before the National Association of United States Pension Surgeons, Washington, D.C., May 13-14, 1903.



introduction of cinchona and quinin into the therapeutics of malaria.

When the Spaniards, under Pizzaro, conquered Peru, they became acquainted with this remedy from the "tree of health," which had been known to the natives from time immemorial. The Viceroy del Cinchon, whose wife was cured by this remedy, gave to it the name of cinchona, but the real credit of having introduced the remedy into Europe is due to the physician of this prince, whose name was Juan del Vego. In England Sydenham was largely instrumental in disseminating knowledge concerning cinchona, and it was he who first emphasized that the remedy must be given in the interval between the attacks, in order to prevent the following attack. In recent time much has been done to make malarial regions healthy by drainage, laying dry of swamps, and improving the condition of the soil, and special efforts directed toward the destruction of mosquitos.

Referring once more to the first period, it is necessary to state that Hippocrates had described fevers "without demonstrable localization" in the section on the "Nature of Man," chapter XVI. He says: "There are four kinds of fever, in addition to those which occur with distinct pains. Their names are synochic fever, daily fever, tertian fever, and quartian fever." In his aphorisms, 21 and 22, he even emphasizes that certain characteristic fevers are distributed upon certain times of the year. In chapter VII he refers to the infectiousness of water coming from swamps. "Whoever drinks it," he says, "must have, during the entire time, a large, consistent spleen." Bellos, of Athens, confirms a complete identity between the fevers described by Hippocrates and those which are found at the present day in Greece.\*

After the discovery of the malaria parasite by Laveran in November, 1880, his results have been confirmed in every country of the world where malaria is known. The names of Golgi, Marchiafava, Celli, Grassi, Feletti, Bignani, Bastianelli, Romanowsky, Di Mattei, are intimately associated with the development of the etiology and parasitology of malaria. Most valuable contributions to this subject in America have been made by the author's teacher, William T. Councilman, Osler, Thayer, Hewetson, Craig, James Ewing, and C. F. Craig.

*Chronic Malaria.*—By chronic malaria we under-

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Bull. de l'Acad. de Méd., 2 Ser., 12, 1883.

stand an infection of the organism with malaria parasites, extending through months and years. After Ross, under the direction of Manson, had shown that certain infections in birds, due to sporozoa, are caused by the sting of mosquitos, Grassi established the fact that the malarial parasite of man is also acquired by the sting of mosquitos. It is at present believed that the mosquitos have infected themselves by previously stinging human beings afflicted with malaria, and sucking in their blood. There is no other source of infection. The mosquitos that transmit this infection belong to the genus anopheles, and they infect man with the youngest developmental stage of the malarial parasite. In the following account I will not use a specific name for this organism, for there is as yet no agreement concerning the terminology. Romberg<sup>1</sup> speaks of "sporozoids;" Laveran and a great many of his followers use the term "plasmodium;" Welch, the term, "*Hæmatozoon falciparum*," etc. There are many other names which are listed in Mannaberg's work on malaria;<sup>2</sup> I shall prefer to speak of the organism here simply as the "malarial parasite." There is no doubt at the present time that this organism is the specific cause of malaria, and that it is acquired by the sting of the mosquito. It is not yet decided among special workers whether there are several species of this same parasite. The best workers, however, consider that the phenomena of the disease are more easily reconciled with the existence of a single polymorphous species.<sup>3</sup> Mannaberg,<sup>4</sup> accepts the view of Celli, Bignami, and Marchiafava, in respect to the separate nature of the malignant tertian and a quotidian group of parasites. Charles F. Craig<sup>5</sup> also divides the parasites producing these fevers into quotidian and tertian. W. S. Thayer, in a recent personal communication to me, expresses the belief that the estivoautumnal fevers are all due to one and the same parasite.

In a practical consideration of chronic malaria a detailed consideration of the parasitology of the disease is out of place. By chronic malaria I do not understand, necessarily, that the continuance of the infection is due to frequent reinfection, but to the stubborn persistence of the parasites which have once entered. If careful statistics of all malaria diseases as they occur in hospitals and camps could be established, I believe that we would discover that the majority of malarial infections have a chronic character; for among the acute malarias we can only class such cases in which the

patients are finally and radically cured after few attacks, whereas those cases which are characterized by four or more relapses are in the majority. Such cases may extend over 6 or 8 weeks, and still they are acute. In order to designate a special case as chronic, it will have to extend over several months. Without the use of quinin the majority of malarial infections would inevitably become chronic.

If we accept, for the sake of argument, the classification of Mannaberg,<sup>6</sup> of malarial fevers into 2 groups: First group, fevers caused by the ordinary malarial parasite (the tertian and quartan parasite of Golgi) without the occurrence of half-moons (crescents), and the second group, fevers caused by the parasites forming the half-moon (he has also a third group due to mixed infections, and a fourth group which he entitles masked fever)—we may say that the malarial infections of the first group rarely become chronic if they receive proper treatment. The principal contingent of the chronic malaria is supplied from the infections with the second group (those with crescents in the blood). Although it is, as a rule, possible to cure radically malarial infections by the correct use of quinin, a complete eradication of the parasites from the organism is frequently impossible. Quinin therapy, and hygiene, and diet, can accomplish practically nothing in this guerilla warfare, when the parasite is entrenched in the tissues of the parenchymatous organs. It is only when the enemy leads his hordes into the free circulation that quinin can overwhelm them. Consequently we find that chronic malaria is much more frequent in those countries where the parasites of the second group predominate, and not so frequent where only the parasites of the first group cause the infection. The parasites of the second group, presenting the crescent or half-moon shapes, cause the most frequent infections during the summer and autumn. These are the estivoautumnal malarial fevers, and they are most likely to become chronic.

The characteristics of chronic malaria, from a clinical standpoint are the following: (1) During many months recurrences of malaria from time to time. These may be typical or masked attacks of chills and fever; (2) anemia; (3) splenic tumor, eventually together with liver enlargement; (4) the same species of malaria parasite is demonstrable in the blood during the entire time; (5) decline of the general constitution. Concerning the nature of the relapses, it is necessary to emphasize that

the patients are frequently not aware of having fever, nor have they a chill, as a rule. Indeed, it frequently happens that patients with chronic malaria, even when they have fever, suffer very slight subjective distress. I have seen malarial patients with the crescents in their blood, splenic tumor and cachexia, who denied ever having had fever. It pays to take frequent measurements of the temperature of such patients before crediting their statement of the absence of fever. It is the chronic form of malaria which is most frequently latent, and which most frequently leads to pernicious malaria. To those who have occasion to see soldiers returning from Cuba, Porto Rico, or the Philippine Islands, the following clinical picture is a familiar one: The soldier enters a hospital, the diagnosis occasionally being that of masked typhoid fever. He has a slight splenic tumor, is anemic, pale, weak and nervous. In about 10 days he seems convalescent, and is directed to leave the hospital. Just about this time he is attacked by violent fever, which is repeated every third day until treatment succeeds in suppressing it by quinin. The patient again becomes anemic, and the splenic tumor enlarges. Once more he seemingly improves, though it takes longer this time than it did after his first admission to the hospital. Convalescence will not progress very far, however, before he has a second relapse. This may repeat itself and continue with alternate improvement and exacerbations for many months. Such soldiers who were admitted in July or August will be found with periodic attacks of fever still in the hospital during the following spring. It may happen that the soldier at this time is discharged, and returning to his home gradually appears to improve, but still showing the evidences of malaria. Cases are on record in which such patients have suddenly collapsed at their homes in a comatose condition. As the physician who is then called in, knows nothing of the preceding history, the case presents diagnostic difficulties. It has happened that such patients have died in these comatose attacks, and only the autopsy revealed the true nature of the chronic malaria infection. On the other hand, cases of complete recovery after such comatose attacks are on record, and the patient may remain well for the rest of his life.

I am requested to speak also on the complications and sequelae of malaria. What is a complication and what is a sequela? (a) A complication is a diseased condition coexistent with and modifying another, with which it



may or may not be etiologically connected. (*b*) A sequela is a consequence of an abnormal condition—any abnormal state following an attack of disease or injury. The difference between the two is considerable. A complication is coexistent with malaria, and a sequela follows it. For instance, splenic tumor and anemia are as a rule complications, but hypertrophy of the heart is as a rule a sequela, and not a complication. In textbooks on malaria you will meet the most striking confusions of these two terms. Malarial cachexia is also a sequela, and not a complication.

The complications involve the following organs in the order stated with greatest frequency: 1. (*a*) Complications of the digestive tract; (*b*) genitourinary system; these two systems are involved with equal frequency. 2. Of the heart and blood vascular system. 3. Of the respiratory system. 4. Nervous system. 5. Diseases of the bones, muscles, and joints. 6. Diseases of the skin. 7. Diseases of the lymphatic system. 8. Diseases of the organs of special sense. 9. Diseases of metabolism—notable among these are diabetes and amyloid degeneration.

You will notice in this tabulation that I have not mentioned the diseases of the blood itself, which, no doubt, should be mentioned first, if we wish to consider it a complication. But malaria itself is from the very beginning a disease of the blood, and we cannot consistently designate as a complication what really constitutes the disease itself. Occasionally it is difficult to hold apart the complications and the sequelæ. Some of the conditions stated may be complications and sequelæ at the same time. It is doubtful whether diabetes mellitus and insipidus deserve the place of genuine complications of malaria. I have a record of 198 analyses of urine of malaria patients gathered from hospitals, and found only two with diabetes mellitus. The coincidence of the 2 diseases can hardly be considered more than accidental. The same can be said of amyloid degeneration. For our special point of study, only the most frequent complications are of importance, those of the digestive organs, the respiratory organs, circulatory and renal organs. The conditions of the blood can appropriately be considered under the heading of malaria cachexia.

*Complications of Digestive Tract.*—The complications of malaria with typhoid fever can only be substantiated by the demonstration of the simultaneous presence of the typhoid bacillus and the malaria parasite in the

same individual. The coexistence of the two infections is reported by Barker and Thayer, and published in the works by Osler and Gilman Thompson. It was J. J. Woodward' who first used the term "typhomalarial fever," by which he conceived a third or hybrid form of fever not identical with malaria or typhoid. Smart, who worked over the material of J. J. Woodward, found that actually 80% of the cases classed as typhomalaria were nothing else than malarial remittent. With our present clinical methods, which establish beyond a doubt the existence or nonexistence of malaria by blood examination and the Widal reaction, there should be no confusion on these points. It was occasionally noticed that an intermittent fever followed in the course of the continuous fever of typhoid—that this intermittent fever was even preceded by chill and ended in sweating. This gave rise to the belief in the union of typhoid fever and malaria. At present we know that these fevers are typhoidal or sequelæ to typhoid fever, and that malaria has nothing to do with them.

*Association of Dysentery with Malarial Fever.*—Numerous of our soldiers, returning from tropical countries are found suffering both from dysentery and malaria. About 15 years ago a vehement polemic filled the journals as to whether malaria *per se* could cause genuine dysentery. It is now known that in this association we have to do with two distinct infections. One with malarial parasite, and the other either with *Amœba coli*, or one of the forms of *Bacillus dysentericus*. It is self-evident that if a patient is already afflicted by one of the forms of dysentery a very slight attack of estivo-autumnal malarial fever may prove pernicious to him. The thing to do in these cases is promptly to ascertain the nature of the dysentery and remove it by high colon irrigations of tannin and quinin, and at the same time to get a clear insight into the nature of the malarial infection by thorough examination of the blood, and treat it by quinin, hypodermically if necessary. For if the patient is simultaneously afflicted by an acute intestinal infection like dysentery, it has been my experience that he frequently rejects the quinin if given by the stomach, and in some cases even when it was retained it did not act as it should have done, because of the deranged gastric chemistry, intestinal putrefaction, diminished gastrointestinal absorption and rapid propulsion of the drug through the gastrointestinal tract. In fact I no longer wait until the stomach rebels, but

start from the beginning by giving .065 gm. (1 gr.) of quinia hydrobromate hypodermically four times a day. In case of soldiers returning from the Philippine Islands, as observed at the United States General Hospital of San Francisco, 65% showing the estivoautumnal parasites in the blood were also suffering from acute and chronic dysentery. Of these about 10% were suffering from amœbic dysentery, as evidenced by the presence of *Amœba coli* in the stools. It is necessary to emphasize that the blood in every case of dysentery coming from malarial and tropical regions (we are specially interested in Philippine Islands, Porto Rico and Cuba) should be examined for the malarial parasite, and the stools for the presence of *Amœba coli* or one of the varieties of *Bacillus dysentericus* of Shiga and Flexner. It is not stated in the report of the United States General Hospital in how many cases the dysentery was found to be due to *Bacillus dysentericus*. In this connection it is necessary to call attention to the fact that dysentery may occur as a complication of malaria, and yet not be due to *Amœba coli*, nor even to *Bacillus dysentericus*, but to actual destruction of the mucosa of the colon by the malarial parasites. That gastric ulcers may be due to malaria was pointed out by me years ago.<sup>8</sup> Marchiafava and Bignami<sup>9</sup> assert that gastric ulcers are found which are due to the malarial condition, in malarial cachexia and amyloid degeneration. Naturally if the malarial parasite can destroy gastric tissue in this way, it can have the same effect on the structure of the colon. These Italian authors assert that in cases of chronic malaria with frequent relapses there are sanguineous diarrheas, which may persist after the malarial attack, and finally present the clinical form of ulcerative enteritis. I have dwelt upon the association of typhoid fever, diarrheas and dysentery with malaria, not because these are the most frequent complications, as proved by statistics, but because, excepting the case of typhoid fever, they are the most frequent complications as presented in our soldiers returning from Cuba and the Philippines.

It is practically impossible to recognize malaria without having acquired the skill in examining the blood for the malaria parasite. It does not require, however, much training to be able to recognize the more significant forms of the malarial organism. For the methods of examination the author refers to the article by W. H. Welch and Wm. S. Thayer in the "Loomis-Thompson System of Medicine;" to the valuable monograph of W.

S. Thayer on this subject, entitled "Lectures on Malarial Fevers;" see also, Thayer and Hewetson,<sup>10</sup> "The Malarial Fevers of Baltimore;" also the work of Geo. M. Sternberg on "Bacteriology;" the article by James Ewing,<sup>11</sup> "Malarial Parasitology," and the scholarly contribution to this subject by Marchiafava and Bignami in the "Twentieth Century Practice of Medicine." I shall come back to this in the paragraph on the "Diagnosis of Chronic Malaria," but this much I must emphasize right here, that in addition to the ability to recognize the malaria parasite, the physician must also be able to recognize the various microorganisms that might cause dysentery, especially *Bacillus dysentericus* and *Amoeba coli*. In order to be able to distinguish typhoid fever, the execution of the Widal test is indispensable. It may not be absolutely necessary for a pension surgeon to be able to execute all of these tests personally, but he should be at least able to recognize the malarial parasite itself; the Widal test and the cultures for *Bacillus dysentericus* may be left for the trained bacteriologist. But to show what dangers may arise from inability to recognize the malarial parasite, the following is quoted from the work of Chas. F. Craig, "Estivoautumnal Malarial Fevers." At Chickamauga Park, where his first work was done, hundreds of cases of typhoid fever, pure and simple, were diagnosed as remittent malarial fever, and treated as such, this being due very largely to the belief that the camp must necessarily become infected by malaria, because it was located in the South. As a matter of fact, there was but very little malaria present among the troops at Chickamauga Park, as was amply shown by the investigations of Vaughau, Dock, Reed, Shakspeare, and others. The colossal mistake of diagnosing hundreds of cases of typhoid fever as malaria was really responsible for causing the terrible epidemic which caused the evacuation of the park as a camping site, and Craig has attributed this mistake to ignorance of the nature and methods of diagnosing the remittent malarial fevers. Even at the risk of becoming redundant, I cannot suppress the desire of again emphasizing the infinite importance of blood examinations by the physician himself. I have very frequently noticed that physicians who did not have the training, confidence in themselves, or desire to do microscopic work, became intensely interested in blood examinations when they were instructed by capable teachers.

*Complications Involving the Spleen and Liver.*—In



patients who have suffered from chronic malaria, a condition known as hypertrophic malarial hepatitis, in which the organ is sometimes enormously enlarged, the spleen similarly becomes enlarged, and the simultaneous enlargement of these 2 organs constitutes an almost constant symptom of chronic malarial infection. In old chronic malaria patients the spleen may become so enormous, that it may occupy the larger part of the left half of the abdomen. There may be perisplenic and perihepatic inflammations eventuating in fibrous adhesions. These changes in the liver and spleen have recently acquired additional significance in the etiology of a complication first described by Banti as "splenomegalie with liver cirrhosis, and disorganization of the blood." It has been pointed out by several authors that chronic malarial infection of the spleen may give the first incentive to the formation of poisonous substances in the spleen which may cause the cirrhosis of the liver and also the disorganization of the blood. The point to bear in mind is that Banti had clearly demonstrated that there are primary diseases of the spleen which, in a very peculiar way, may lead to toxic infection of the entire organism.

*Splenomegalie with Liver Cirrhosis and Disorganization of the Blood; Banti's Disease.*—Although not all cases of this complication which are on record have been attributed to chronic malaria, I consider it necessary to include this complication here because in 2 cases which I observed, it occurred in individuals who had been in malarial countries, one of them a soldier who had served in the Cuban campaign, and had an unmistakable history of chronic malarial infection. In Osler's report on "Anæmia Splenica,"<sup>12</sup> he gives a record of 15 cases that have been carefully studied. In five of these, that is, one-third of the cases, there was a history of malaria. The term, "anæmia splenica," was originally used by Griesinger, after it was discovered that leukemia need not necessarily be associated with a large spleen. Banti<sup>13</sup> described a splenomegalie with cirrhosis of the liver occurring in young individuals, and in the etiology he excluded malaria, syphilis, alcohol, and other intoxications, and seemed inclined to admit only digestive disturbances as predisposing factors. The condition begins with a primary swelling of the spleen, which is followed by anemia and cachexia, and a chronic inflammation of the liver tissue, which in its final stages may present the clinical and pathologic characteristics of

Lænnec's cirrhosis. The blood of these patients shows marked diminution of the red blood corpuscles, moderate poikilocytosis, no leukocytosis during the course of the disease, hemorrhages may occur especially from the gastrointestinal tract, edema, dyspnea, in some cases ascites and icterus. In the beginning the urine is normal, and later on shows urobilin and bilirubin.

The anatomic basis of Banti's disease is a trabecular and follicular hyperplasia of the spleen (in later stages an extensive fibrinous transformation of the splenic pulp develops).

The splenic vein (lienal) showed atheromatous changes in one of my patients, an individual 22 years old. In the liver inflammatory foci were evident in the parenchyma around the portal vein extending into the interlobular spaces—eventually this presents the typical picture of portal cirrhosis. The prognosis is grave, and the disease terminates fatally in 5 or 6 months, unless an extirpation of the spleen is successful.

Banti conceives this complex to be a direct intoxication, which is caused by toxins originally formed in the diseased spleen, and are first of all conducted to the liver with the portal blood, there acting as local inflammatory irritants, and furthermore as destructive of the protoplasm of the blood cells.

The direct proof of the validity of this view is furnished by a report of complete cures that have occurred after the extirpation of the spleen (splenectomy). These recoveries followed even in such cases in which signs of cirrhotic contraction of the liver were evident at the operation. These statements of Banti have in principle been confirmed by other investigators, especially the conception that it is a primary disease of the spleen (see Bonardi, Cavazzani, Tenile, Rinaldi, Maragliano, Benvenuti, Sciolla, Sippy, who partly report clinical and partly operative cases).

A number of investigations have been made with a view to determining whether bacteria are active in the production of the primary splenic infection, but neither in the juice of the spleen nor in the blood could bacteria be demonstrated. Senator, Sippy, Sciolla<sup>14</sup> have conducted investigations in this direction. Their negative results indicate that the exact nature of this disease is unknown. It is probably not an infective disease, but rather a chronic intoxication caused by an unknown poison. Harris and Herzog<sup>15</sup> suggest that a chronic hemolysin is produced by an enzyme manufactured by

the endothelial cells of the spleen. Banti seemed to favor the view that disturbances in the digestive tract were predisposing factors. As in a third of Osler's cases, and both my cases, there was a distinct history of malaria, this would impress the necessity of going over the entire reports of cases of this kind to determine whether malaria is really not more than an occasional cause. Of course, there are cases like that of Dr. A. D. Atkinson,<sup>16</sup> in which there was no history of malaria, and as a blood examination was made in most all of the cases, it is not probable that the malaria parasite would have escaped detection had it been present. On the other hand, we must not overlook the fact that chronic malarial of long-standing antecedents, may have produced decided detrimental effects upon the splenic tissues, and the parasite been eradicated by quinin treatment. This was the status in one of my cases; a youth of 27 had a history of chills and fever in April and May, 1900. The malarial parasite was then found in the blood, in Richmond. But when I examined him in March, 1903, no malaria parasite could be detected either by myself or by two other competent clinicians. So that the important point about the factor of chronic malaria in Banti's disease is a scrutinizing inquiry into the previous history of the patient. From a number of the publications on the subject, it is evident that the cirrhosis of the liver is not necessarily pronounced in all cases, and consequently ascites is not always one of the phenomena. It may occur, however, in the absence of evidences of liver cirrhosis, as a result of the passive congestion caused by the splenic swelling, or as a result of the anemic state of the blood. According to Senator, the ascites may be due to obstructions of the lymph channels by simultaneous swelling of the mesenteric glands. Gilbert and Fournier,<sup>17</sup> in discussing the relation of the swelling of the spleen to the inflammation of the liver, suggest that both organs may be simultaneously infected by the same toxin only that the liver infection develops slower than that of the spleen. The most characteristic symptoms are those referring to hemorrhagic diathesis. Osler, as well as Senator, has emphasized that gastrointestinal hemorrhages are very frequently observed, but hemorrhages from the mouth and nose and urinary tract are also frequent, and Osler has observed cutaneous melanosis similar to that occurring in pseudoleukemia.

From the cases compiled by Sippy and Osler,<sup>18</sup> I think the conclusion is justifiable that the results of the blood examinations are quite uniform. Stating it in a general

way, these may be stated as follow: Moderate or severe anemia with reduction of the number of red corpuscles; a further reduction of the amount of hemoglobin (out of proportion to the reduction of the erythrocytes); small number of leukocytes (leukopenia); sometimes normal relations between the different forms of blood cells; at other times moderate presence of lymphocytes.

Banti's conception of this complex of symptoms for which Osler prefers the name of "*anemia splenica*," really stamps this as a pseudoleukemic disease, a chronic infection of the general organism, originating in the glandular swelling, with this difference between pseudoleukemia and Banti's complex: In pseudoleukemia we have a progressive involvement of new groups of glands, but in Banti's disease we have an inflammation of the liver tissue. The general intoxication in both diseases is expressed in the cachexia, anemia, edemas, hemorrhages. It is especially interesting to be able to demonstrate that the formation of the infective toxins occurs primarily in the spleen because in 19 cases of extirpation of the spleen collected by Harris and Herzog<sup>20</sup> recovery followed in 14, and in one the result was not given. In Cases IV and V of Osler's compilation the spleen was removed by Dr. Harvey L. Cushing. In Case IV the patient was reported well 4 years after the operation (information from a private conversation with Dr. Cushing). In Case V the patient died of an esophageal varix.

According to Osler and Cushing, all cachectic symptoms disappeared after removal of the spleen, and Bessel-Hagen,<sup>21</sup> Maragliano Terrile emphasized that the spleen should be removed as soon as the nature of the disease is recognized, and clinicians should by no means wait until an irreparable general condition and a severe cirrhosis have been produced. If a comparison to pseudoleukemia is permissible, we might suggest that all suspicious lymph-gland tumors should also be removed as soon as the pseudoleukemia is recognized. As a result we might also comment on the influence of the removal of the spleen on the cells of the blood. Numerous careful observations by various competent authors have failed to demonstrate that splenectomy has any influence whatever in producing changes in the red or colorless blood-corpuscles. This is in agreement with the views of Ehrlich and Lazarus, who attribute no active influence to the spleen in the production of the normal blood cells. It is of further interest to note the diametrically opposite effect that splenectomy has had on the condition of the blood known as leukemia, in which the result



was extremely unfavorable or fatal. This demonstrates a fundamental difference between the pseudoleukemic and spleen diseases, and those depending on a leukemic basis. In the former, including Banti's disease, the gland and spleen changes are the primary element in the disease process, whereas they are only secondary complications of diseases of the bone marrow in leukemia.

*Diseases of the Nervous System.*—Coincident with the estivoautumnal fevers there may occur attacks of acute mania, and such cases have been described by Yanarris,<sup>22</sup> but this complication is very rare. Hysteria is not a very uncommon complication in nervous women and even in men, and as in hysteric attacks in general, the symptoms complained of vary greatly in character and severity. Paraplegia and hemiplegia may rarely complicate these fevers, and neuroses of various kinds are not uncommon. Meningitis may also occur.<sup>23</sup>

*Diseases of the Respiratory System.*—Both lobar and lobular pneumonia occur as complications, the first being by no means a rare complication. Early observers held that the pneumonia accompanying malaria was directly due to malarial poison; but recent investigations have proved conclusively that the malarial parasites, *per se*, are unable to produce a true pneumonia. The pneumonia complicating malaria will always be found, upon bacteriologic examination, to be due to *Diplococcus pneumoniae*.

There is a form of pernicious estivoautumnal fever in which the symptoms are chiefly referred to the lung, and are identical with those of lobar pneumonia. The condition present in these cases is due to a localization of the parasites in the lung capillaries. Microscopic examination of the lung in such cases shows that the lesions present differ widely from those common to lobar pneumonia.

Pneumonia may complicate the malarial infection at any time, and may develop suddenly or insidiously. The course of the pneumonia is generally but little altered, although the disease is apt to assume a more severe type than when it occurs alone. Pneumonic symptoms may entirely mask the malaria, or on the other hand, may be so slight as to be masked by the malarial infection.

The prognosis in pneumonia complicating estivoautumnal malaria is always very grave, many cases proving fatal. The mortality is stated by Ascoli to be as high as 60% to 78% in patients who have had repeated estivoautumnal attacks. Death may occur in from 36 to 72 hours from the initiation of the attack.

In patients who recover, the convalescence is very slow, resolution being greatly delayed. An empyema may result in rare instances. Not rarely the affected portions of the lung become fibroid, and a chronic fibroid pneumonia results, or a bronchiectasis appears.

Acute bronchitis is a very common complication of the estivoautumnal fevers, being observed in about 40% of the cases. It may be very persistent, and often very markedly weakens and exhausts the patient.

A septicemia due to pneumonic infection has been described by Marchiafava, Bignami, Nazari, and others as complicating malaria.

*Tuberculosis.*—Tuberculosis and malaria may occur simultaneously in the same individual. It is known that both diseases are very commonly associated, and that even fatal cases of estivoautumnal malaria may occur in patients suffering from active tuberculosis. Marchiafava and Biguami have reported a very interesting case of this kind. Marchiafava claims that "if the malarial infection attacks organisms affected by tuberculosis, the latter is not arrested, but acquires a tendency to spread and produces miliary tuberculosis." The same authority states that "according to our experience, malarial cachexia does not predispose to tuberculosis, as do other cachexias." Pleurisy and malaria are sometimes associated, but it is a somewhat rare complication, and when it occurs pursues the same clinical course as usual.

It has been stated that if quinin be administered to a patient suffering from any of the complications mentioned, it will be followed by a cessation of the malarial symptoms, and the complicating process will run its usual course. This is, of course, not invariably the case, for certain forms of chronic malaria do not improve under quinia and again sometimes the complicating process may become much better, as in pneumonia for example.

The diagnosis of estivoautumnal malaria, when its symptoms are masked by complications, is only to be made by the microscopic examination of the blood.

*Diseases of the Circulatory System.*—Those organic diseases of the heart which happen to be present at the time of an estivoautumnal infection will, as complications, render the prognosis exceedingly grave. Acute endocarditis may occur as a complication and the ulcerative form of the disease may follow a pneumonic complication. Functional disorders of the heart are very common complications of the estivoautumnal malarial fevers. A slow pulse during convalescence is common, sometimes counting but 40 to the minute.

*Diseases of the Genitourinary System.*—Nephritis is

one of the most common complications of these fevers, and occurs in about 3% of the cases. As a rule, the nephritis is an acute one, and generally subsides shortly after the cessation of the malarial attack. Nephritis is as much a consequence of malaria infection as it is a complication.

Orchitis and epididymitis are rare complications, but as a rule a history of gonorrhea infection is usually to be obtained. There are no reliable evidences indicating that there is an orchitis due to the malarial poison, *i. e.*, a malarial orchitis.

It is impossible within the short time to which this address is limited to give an exhaustive treatise of all the possible complications and sequelæ of malaria, nor can it be expected that the diagnosis could be fully presented with such regard to detail as the importance of this subject requires. The main object of my report, as I was requested to make it by the president and committee, was to emphasize the relationship between chronic malaria and disturbances of the digestive organs. And even in this regard I am conscious that the paper is incomplete. If I have succeeded in only stimulating your individual thinking, and given an incentive to personal research along these lines, I will be satisfied with the little progress that has been accomplished.

In conclusion I desire to express my appreciation of the honor conferred upon me in the invitation to address your representative body.

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- <sup>8</sup> Hemmeter: Diseases of the Stomach, Third edition, p. 386, "Malaria Complicating Gastric Diseases; also Report of a Case of Periodic Hematemesis Occurring Every Third Day."
- <sup>9</sup> XXth Century Practice of Medicine, Vol. xix, p. 386.
- <sup>10</sup> Johns Hopkins Press, 1895.
- <sup>11</sup> Journal of Experimental Medicine, Vol. vi.
- <sup>12</sup> Transactions of Assoc. of Amer. Physicians, 1902.
- <sup>13</sup> Lo Sperimentale, 1894, also Splenomegalie mit Lebercirrhose, Ziegler's Beiträge, Bd. 21, Heft 1.
- <sup>14</sup> Amer. Jour. Med. Sci., October, 1899.
- <sup>15</sup> Annals of Surgery, July, 1901.
- <sup>16</sup> Osler, l. c.
- <sup>17</sup> La Sem. méd., 1898, p. 141.
- <sup>18</sup> Sippy, l. c.
- <sup>19</sup> Osler, l. c., first paper in Amer. Jour. Med. Sciences, January, 1900.
- <sup>20</sup> Annals of Surgery, July, 1901.
- <sup>21</sup> Deutsch. Arch. f. klin. Chirurgie, 1900, Heft 1.
- <sup>22</sup> La Méd. Orient., 1898, ii, 6.
- <sup>23</sup> The Estivo-Autumnal Malarial Fevers, by Chas. F. Craig, 1901.

# PROGRESSIVE MEDICINE.

DECEMBER, 1903.

## DISEASES OF THE DIGESTIVE TRACT AND ALLIED ORGANS, THE LIVER, PANCREAS, AND PERITONEUM.

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### THE STOMACH.

#### Recent Advances Concerning the Physiology of the Stomach.

The work of Pawlow has shown conclusively that the gastric HCl is the most essential stimulation to the formation of active ferments of the pancreatic juice (no HCl, no or little active ferments in the pancreatic juice). In his masterly research Pawlow discovered a new enzyme in gastric secretion—a specific ferment, *chymaze*—which does not digest food, but which accelerates the action of the ferments of the pancreatic secretion. The digestive tract is not universally and uniformly irritable or stimulatable by every mechanical, chemical, thermic, or dietetic agent, but there is a specific reaction with regard to the peculiarity of every individual digestive demand or duty. There is a most artistic mechanism of digestion revealed by Pawlow's work which in its preciseness and accuracy exceeds any new discovery of modern physiology. If you want to feel proud of being a physician read Pawlow's *Die Arbeit der Verdauungsdrüsen*.

The most efficient means of counteracting *dyspepsia* due to pancreatic insufficiency is to bring about a healthy appetite. Appetite is the stimulus to normal gastric secretion, and this in turn the normal stimulant to healthy pancreatic secretion.

A brief reference to the newer gastric physiology is indispensable, not simply because the stomach is the preparatory organ for intestinal digestion, but also because the chemical processes which various food articles undergo in the stomach are of far-reaching importance for the changes which are to occur in these



foods after they reach the intestines. Many of the older authors, beginning with the American physiologist, Beaumont, believe that the mechanical irritation of the foods cause the gastric secretion, but the experiments in Pawlow's laboratory have proved the fallacy of this view. In the first place, if the secretion were due to simple mechanical irritation, there is no reason why irritation with the point of a glass rod, with a feather, or with sand placed in the stomach should not cause the secretion also.<sup>1</sup> The mistake of the older experimenters, according to Pawlow, grew out of the fact that they ignored the so-called psychic secretion—a secretion which can be set up by the mere smell of food or even by a very intense feeling of hunger. If the œsophagus of the dog is cut, and its end sewed to the edges of an abdominal wound, and at the same time a gastric fistula is established, pieces of meat which are fed to the dog after healing of these fistulae will not reach the stomach, but fall out of the upper end of the fistula leading into the œsophagus. Nevertheless, in five or six minutes after swallowing the food gastric juice begins to be secreted, running from the gastric cannula first in drops and afterward in a continuous stream. If the dog be offered meat without receiving it the gastric secretion will also appear, though not so plentifully as when the dog was actually allowed to eat the meat.

A further interesting phenomenon observed on these dogs was that no secretion followed the swallowing of indigestible substances like small stones. These experimenters, furthermore, elicited the astounding fact that for every kind of food a definite gastric secretion is formed of specific composition. Therefore, we can say that the stomach provides a certain chemical agent to meet each case. We must, therefore, conclude that the mucous membrane of the stomach is capable of distinguishing between the varieties and classes of food that come in contact with it, much as the skin recognizes mechanical, chemical, thermic, and electric stimulation. The question might be asked, "What is the object of this psychic secretion?" for Pawlow has clearly established the existence of two kinds of *gastric secretion*, the *chemical* and the *psychic*. This question applied to the human physiology would be the same as inquiring "What is the object of appetite?" The answer is that under the influence of psychic secretion a gastric juice is furnished which is much more effective than that which is secreted under purely chemical stimulation of the food—*i. e.*, when food is taken without any special appetite. Furthermore, under the influence of psychic secretion foods which otherwise would not stimulate

<sup>1</sup> A secretion can at times be forced by mechanical irritation, but is mostly mucus or a serous liquid, not a gastric juice.

the gastric mucosa to secretion become converted by the already present psychic secretion into something else which constitutes a further stimulant to the secretion of gastric juice. For instance, if a solution of albumen be administered to a dog upon which a Pawlow operation has been performed—*i. e.*, splitting off part of the stomach with all the vessels and nerves intact, and making this second smaller stomach communicate with the external abdominal wall, but not with the general cavity of the large stomach from which it is dissected<sup>1</sup>—there will be no secretion from the small stomach, for albumen of itself does not excite chemical secretion; but if the psychic secretion is set up by some other means before the albumen is placed in the large stomach—for instance, by waving a piece of meat before the dog's eyes—then, following the introduction of albumen, a secretion will be found in the small stomach which is qualitatively and quantitatively greater than the psychic secretion alone or when albumen is given alone. It is evident that whilst albumen of itself does not excite secretion, the products of albumen do cause this secretion. The same is true of pieces of bread which when placed in the large stomach through the fistula will not promote a secretion, but if the dog is allowed to swallow the bread secretion commences and continues for several hours. Psychic secretion, therefore, is a preparatory secretion, converting substances which would otherwise not stimulate the stomach into such substances which can accomplish this stimulation. The fact that bread will cause a secretion whenever chewed and swallowed and not when placed directly in the stomach through the fistula may be interpreted, as Pawlow and Peter Borisssof do, as proving the secretion of a gastric juice under psychic influence; but, as I will show presently, it may be due to a special ferment in the saliva that stimulates gastric secretion.

Further revelations from Pawlow's laboratory disclose very important relations between the various classes of food, permitting the conclusion that they may mutually advance or interfere with the digestion of their various constituents in the gastric chyme. For instance, starch paste does not of itself promote gastric secretion, but when mixed with meat it was found to accelerate the action of the gastric juice, increasing its digestive power. On the other hand, the addition of fat to a meat diet diminished the quantity of gastric secretion as well as its digestive power. Furthermore, it was demonstrated that the stomach is capable of distinguishing between lactic, butyric, and hydrochloric acids, and responded to each of these acids with a varying quantitative secretion. As lactic and butyric acids are products of gastric fermentation, their

<sup>1</sup> International Clinics, Series XII., vol. ii. p. 276.

stimulating influence on gastric secretion is of therapeutic importance. It is evident, therefore, that the stomach is extremely delicate in detecting not only the composition of foods and regulating the composition of its secretion correspondingly, but that it can distinguish between various organic acids. These experiments, furthermore, gave the clue to the treatment of gastric secretory disorders not by drugs merely, but by dietetic measures.

**Methods for Judging the Chemistry of the Stomach; Determination of HCl, Pepsin, Rennin, etc.** In almost every case of disease of the stomach it is a *sine qua non* to obtain a clear insight into the state of the gastric secretion, especially the secretion of HCl, pepsin, and chymozin. There is no strict parallelism between peptic strength and the quantity of HCl in gastric juice. The secretion of the pepsin and other ferments and the secretion of HCl are two different and independent processes, which are influenced in unequal manner by medical agents (atropine and pilocarpine). On the basis of an extensive analytical material, in which the amount of HCl in human gastric juices was determined by the method of J. Sjökvist, and the concentration of pepsin according to the method of Mette,<sup>1</sup> I used the modification of Mette's method as advised by E. Nirenstein and A. Schiff,<sup>2</sup> who, in my opinion, have proven very conclusively that Mette's method is not a practical one to determine the pepsin concentration in human gastric juices unless these juices are diluted by sixteen times their volume. I have become convinced that the quantity of pepsin in a gastric juice and the quantity of HCl rarely run parallel, and even in the same normal individual the same amount of HCl does not necessarily correspond to the same amount of pepsin secreted under the stimulation of the identical test-meal on different days. These remarks are sufficient to emphasize that pepsin secretion and HCl secretion are two different things. The stomach, in fact, has in recent years been shown to contain a versatility of secretion which is astounding. No less than seven different products are formed by the gastric mucosa: 1. We have the secretion of mucus by the cylindrical epithelium. 2. The diluting or aqueous secretion, by which it is capable of diluting the gastric chyme in order to reach a certain consistency most favorable for the gastric digestion. 3. The secretion of HCl. 4. Of pepsin. 5. Of chymozin or rennin. 6. Of gastric lipase, the fat-splitting ferment. 7. Of chymaze, the ferment which Pawlow has discovered to be the physiological stimulant accelerating the action of the ferments of the pancreatic secretion—chymaze does not digest food.

<sup>1</sup> Contribution à l'innervation de la glande sous-stomacale, St. Petersburg, 1889. Original in Russian.

<sup>2</sup> Archiv f. Verdauungs-krankheiten, Band viii. p. 560.



For clinical purposes it is not always practical, even if it were possible, to make quantitative determinations of these varieties of gastric secretions. All of the investigations that were conducted on the physiology of pepsin and trypsin secretion, in the St. Petersburg Institute for Experimental Medicine, by Pawlow, were executed by the aid of Mette's method for determining the concentration of pepsin, and this method I am convinced, after considerable experience with it, is inaccurate and unsatisfactory, even when applied with the modification of Nierenstein and Schiff, to be considered hereafter. The method of Henry W. Bettmann, to be described later, appears to me as being more reliable.

**HCl Determination.** As before mentioned, the method which has proven most practical and at the same time most reliable for determining the amount of HCl in the gastric juice, has in my experience been that of Sjöqvist.<sup>1</sup> With a few modifications this method is available to determine the total acidity, the combined and free HCl. Right here I must remark that even at the present time there is not one single method for determining the amount of HCl in human gastric juice which is absolutely correct from the chemical standpoint. Accordingly it is fortunate for the clinician that it is not necessary for diagnostic purposes to possess such absolutely correct methods. A certain degree of approximative correctness is sufficient for diagnosis. It is for this reason and also because of the simplicity and practicability that Töpher's method of titrating is still so much in vogue, although it cannot claim to give chemically correct results. The total acidity is, according to this method, determined by phenolphthalein, the free HCl by dimethylamidobenzol, and a third indicator, the alizarin sulphonate of sodium in 1 per cent. solution, is sensitive to all acid factors except the combined HCl. If we accordingly know the total acidity and subtract from it the values obtained by alizarin sulphonate of sodium, we will get as a difference the value of the loosely combined HCl. It is essential to have an accurately standardized decinormal solution of sodium hydroxide for these titrations. I am well aware that dimethylamidobenzol, as it is used in 0.5 per cent. solution, reacts to acid phosphates, and to moderate concentrations of lactic acid. Yet in my experience it is a practical method whenever free HCl is present in the gastric juice at all. Whenever there is no free HCl present the method is unreliable. When free HCl is absent by dimethylamidobenzol I recommend the reagent of Günzberg (phloroglucin, 2 gm.; vanillin, 1 gm.; absolute alcohol, 30).

I have also had an extensive experience with tropæolin 00. On heat-

<sup>1</sup> Zeitschrift f. physiol. Chemie, Band xiii. S. 1.



ing tropæolin in saturated alcoholic solution with gastric juice, pinkish or violet stripes develop on the porcelain dish, which are characteristic for HCl. I consider tropæolin is as sensitive a reagent for HCl as the Günzberg or resorcin tests. It is necessary to emphasize that in order to be as accurate as possible the tests should be conducted with several reagents on the same gastric juice. Phloroglucin-vanillin and resorcin are HCl reagents in the proper sense of the word, and do not react to any other acid.

G. D. Spinneau has invented a so-called *gastro-acidimeter*, by which the total acidity of the gastric contents can be determined in 1 c.c. of the filtrate. The instrument, which is purchasable from Franz Müller, in Bonn, is made of glass, and costs 30 M. As there is no dearth of methods for determining the total acidity, this expensive instrument seems entirely dispensable.

**The Quantitative Estimation of the Pepsin ; Determination of the Digestive Power of Gastric Juice.** Nothing could be more misleading than the assumption that even the most accurate determination of the amount of HCl secreted would give us an exact insight into the digestive work performed by the stomach. We must not lose sight of the fact that normal proteolysis requires pepsin for its perfect execution, and that HCl alone can bring the proteid no farther than the stage of acid syntonin. And, furthermore, that the different products or constituents of the gastric secretion are expressions of different secretory activities of the glandular parenchyma, and, as has been made probable by the investigations of Pawlow, they can only be evoked by specific dietetic stimulants and in my opinion are each under the influence of a special nervous control. In a publication in the *Medical News*, N. Y., June 7, 1902, on "The Use and Abuse of Digestive Ferments," I described an interesting case in which the amount of free HCl was equal to 60,<sup>1</sup> and yet the pepsin seemed to be reduced, for albumen digestion did not take place satisfactorily until pepsin was added to the digesting mixture.

I have since then studied this same and two other similar cases giving an excessive amount of free HCl by the methods of Hammerschlag and Mette for the determination of the concentration of pepsin. While the amount of pepsin is generally assumed to increase parallel with the amount of HCl secreted, these three cases gave evidence of a disproportion between the increase of the pepsin and HCl secretion. Schwan was among the first to show that an excess of HCl may actually inhibit proteolysis. As the action of ferments is arrested by the presence in excess of their products, this was thought to be one of the causes of

<sup>1</sup> 60 c.c. of  $\frac{1}{10}$  normal solution of NaOH to neutralize 10 c.c. of gastric juice.

the inhibited pepsin digestion with excessive HCl secretion. This view is based on the assumption that an excessive HCl secretion goes hand in hand with an excessive secretion of pepsin. It is evident from the case which I have reported in the *Medical News*<sup>1</sup> that reduced pepsin proteolysis may be due to an insufficient amount of pepsin, for when pepsin was added to this gastric juice the digestion of a weighed amount of albumen became normal. It is conceivable that impeded proteolysis may be due as well to an insufficient as to an excessive amount of pepsin. What is needed is a normal pepsin concentration, and this probably varies for each diet and very probably in each individual. I must here emphasize that our methods of determining the concentration of pepsin have up to the year 1902 been very defective; and this explains why so little has been known concerning the exact and normal relations between the quantity of pepsin and the quantity of HCl, and why available practical deductions for diagnosis have not been numerous. It will be necessary for me to go into the consideration of the most recent methods for the determination of pepsin concentration, those of Hammerschlag and Mette; they are of limited practical value for diagnosis, because they are not absolutely accurate.

The physiological digestion of albumen in the stomach is dependent upon a variety of factors, the better known of which are the following:

1. Upon the amount of free HCl. The most favorable amount is equal to 0.2 per cent. of free HCl.
2. Upon the amount of pepsin. The intensity of albumen digestion increases up to a certain limit as the amount of pepsin increases, and it is said to be proportional to the square root of the pepsin concentrations (law of Emil Shütz).
3. Upon the nature and density of the kind of albumen to be digested. Fibrin, which swells up readily, is digested quicker than coagulated egg albumen, and native albumen is digested more readily than coagulated albumen; animal albumen easier than vegetable.
4. Upon the temperature. Gastric juice acts best at a temperature of about 38° to 40° C. At zero the digestion becomes arrested, and at +80° pepsin is destroyed.
5. Upon the presence of the products of albumen digestion. As already stated, all fermentative hydrolytic (catalytic) processes are arrested by the presence of a certain amount of the products of fermentation. The inhibiting influence of the products cannot be removed in artificial digestion experiments, as they can and are during the normal gastric digestion, where a certain equilibrium of relation is maintained between the amount of HCl and pepsin which is continually secreted and the amount of products which are removed either by gastric absorption or by peristaltic expulsion into the duodenum. It

<sup>1</sup> Loc. cit.

is quite certain, also, that the products of albumen digestion can chemically combine with the HCl during artificial digestion experiments to a degree which does not occur in the normal gastric digestion. These difficulties constitute the greatest stumbling block toward the exact experimental imitation of gastric digestion in glass vessels, where we cannot continually keep on adding HCl nor keep on removing the products of digestion. 6. Finally, albumen digestion is dependent upon the presence of certain salts which may prevent the loosening of the proteid to be digested, or they may precipitate the pepsin. Incidentally it should be remarked here that strong concentrations of alcohol may produce these same effects. The presence of small quantities of sodium chloride and phosphates is harmless, but the presence of urates and sulphates is detrimental.

HAMMERSCHLAG'S METHOD OF DETERMINING PEPSIN CONCENTRATION. Take a 1 per cent. solution of egg albumen and add sufficient HCl that it shall contain four per thousand of *free* HCl. (I notice in some text-books and publications that the directions call for 3 to 4 per cent. HCl without stating that the acid should be free.) Measure off two samples each containing 10 c.c. of this albumen solution. To the one 5 c.c. of the gastric juice to be examined is added; to the other, which is used as a control, 5 c.c. of distilled water is added. From each of these samples a definite quantity is poured into each of two Essbach albuminometer tubes up to the mark U. Then the two digesting mixtures are put in the incubator at body temperature for one hour. After this time the tubes are filled with the Essbach reagent up to the mark R. Each tube is tightly corked and allowed to stand twenty-four hours at room temperature after shaking them by inverting them several times. After this the height of the sediment can be read off in both tubes. The control tube, to which nothing but water has been added, shows the original percentage of albumen of the mixture, and the difference in the sediment of this tube and the second tube to which gastric juice has been added is equal to the amount of albumen that has been digested. According to Hammerschlag's statement, between 80 and 95 per cent. of albumen is digested in this manner by the gastric juice from healthy individuals.

METTE'S METHOD FOR DETERMINING PEPSIN CONCENTRATION. The white of fresh hen-eggs is drawn up in fine glass tubes having a lumen of 1 mm. to 2 mm. This egg albumen is coagulated at a temperature of 95°. From these albumen tubes pieces are cut out 2 cm. long, placed in porcelain dishes, and covered with the gastric juice to be tested. These digesting mixtures are placed in the thermostat for twenty-four hours.



Nierenstein and Schiff<sup>1</sup> have shown that the digestion is fairly uniform during twenty-four hours. Accordingly the amount of the albumen column digested in twenty-four hours is twice as large as that digested in twelve hours. The amount of coagulated albumen digested in the little glass tubes is measured by a steel scale graduated in 0.1 mm.; an enlarging lens or dissecting microscope is advantageous for this purpose. According to the law of Borisow,<sup>2</sup> the lengths of the albumen columns digested bear the same relations to each other as the square roots of the pepsin concentration. In other words, the pepsin concentrations are in proportion to the square of the millimetres of the albumen columns digested. For instance, if 2 mm. and 3 mm. of albumen columns are digested in two solutions respectively, the relative amount of pepsin are to each other as 4 is to 9 (not as 2 is to 3).

Of these two methods Mette's gives more exact results than Hammerschlag's, though both methods are not as exact as we have a right to demand, for with standard albumen solutions of known strength they both give variable and incorrect results.

The chief defects of Hammerschlag's method are : 1. The Essbach method which it makes use of is itself notoriously inaccurate. 2. The picric acid solution precipitates not only the albumen, but peptones and albumoses. 3. The test requires twenty-four hours. Mette uses capillary tubes filled with coagulated egg albumen. He lays pieces of such tubes in the juice to be examined and estimates the digestive power of the juice by the amount of the albumen digested after ten hours. As ordinarily made with undiluted gastric juice, this method is entirely unreliable. In weakly digesting or diluted gastric juices the technical errors may amount to from 10 to 30 per cent.

A new method of determining the digestive power of gastric juice, suggested by Dr. Henry Wald Bettman,<sup>3</sup> is as follows : A circa 0.75 per cent. solution of albumen containing 0.2 per cent. free HCl is used ; 10 c.c. of this solution is mixed with 5 c.c. of the gastric juice, brought in certain cases to an acidity of 0.2 per cent. The mixture is placed in the incubator at 37° C., a control solution mixed with 0.2 per cent. HCl accompanying it. After exactly one hour the two tubes are removed, the albumen is precipitated with a 10 per cent. solution of trichloroacetic acid, and the tubes centrifugalized in a high-speed centrifugal machine. The difference in volume of the two sedi-

<sup>1</sup> Archiv f. Verdauungs-krankheiten, Band viii. p. 569.

<sup>2</sup> This law was not original with Borisow, but was discovered in 1895 by Emil Schütz, A Method for Determining the Relative Pepsin Concentration. Zeitschrift f. physik. Chemistry, 1895, Band ix.

<sup>3</sup> American Gastro-enterologic Association, May 14, 1903.



ments gives the amount of albumen digested. The test can be completed in two or three hours. The range of error is very small.

When the albumen digested is determined according to the method of H. W. Bettman or A. L. Benedict, and on the same specimens the amount of free and combined HCl is determined, it will be found that the presence of free HCl in a gastric juice does not by any means mean that this gastric juice digests well. I have personally reported cases of excessive hyperchlorhydria where the albumen digestion was under the normal. I do not think that this discrepancy is due to any defect in the methods employed, but that it suggests that the pepsin secretion and HCl secretion are two entirely different things, and that one secretion may be abnormally increased at the same time that the other is abnormally diminished. There is room for individual interpretation of this discrepancy, however, and it may be that the proteolysis in hyperchlorhydria, which is at first rapid, may be later on arrested by its own products.<sup>1</sup> In some of the cases which I have studied in this way, however, the proteolysis was resumed in the digestion mixtures after I had added very small quantities of pepsin. This

suggests, of course, that there are rare cases in which pepsin has a distinct field of therapeutic usefulness, and that we are justified and warranted in adding it to gastric digestion of such cases in which a direct correlation can be established between the amount of free HCl and the amount of pepsin concentration. Such an indication for pepsin is very rare, and can only be ascertained by repeated and painstaking analyses.

**Gastritis.** A case of diffuse *phlegmonous gastritis* is reported by Lengemann<sup>2</sup> which was cured by operation, thus confirming my predictions given years ago<sup>3</sup> that the only correct way to treat such cases is by operation.

**Gastric Ulcer.** There have been no noteworthy advances in our knowledge of the pathogenesis of peptic ulcer since the publication of the experiments of B. Fütterer.<sup>4</sup> The essential point of these investigations was that experimental gastric ulcers in animals would, as a rule, heal very promptly unless the hæmoglobin was destroyed by the injection into the circulation of pyrogallie acid. The disorganization of the hæmoglobin, therefore, is one of the conditions for the maintenance of gastric ulcer, and the treatment must be directed toward keeping up the hæmoglobin to the normal standard. This is done by the administration of beef-juice according to the method of Fütterer,<sup>5</sup>

<sup>1</sup> Hemmeter. Diseases of the Intestines, vol. i. pp. 114-116.

<sup>2</sup> Mitteilungen aus d. Grenzgebieten d. Med. u. Chir., Band ix., Heft 4 und 5.

<sup>3</sup> Hemmeter. Diseases of the Stomach, 1st edition, 1897.

<sup>4</sup> PROGRESSIVE MEDICINE, December, 1902, vol. iv.

<sup>5</sup> Ibid., p. 32.

which, in my experience, is indeed efficacious as long as the patient does not develop a repugnance against this preparation. Where the patient finally objects to this diet I have sometimes succeeded with his enemias of ferratin.

In connection with the dietetic treatment of gastric ulcer remarks are necessary which are applicable to the dietetic management of all irritative states of the gastric mucosa. Modern research confirmed the view that the digestive work of the stomach is not only in the mechanical and to a certain extent chemical digestion and not in the solution of the food. This gives the key to the dietetic management, viz., all foods should be given in so divided a state that the large part of the work is done by the stomach. As the stomach must dissolve the connective tissue of meat (the pancreas and intestinal juice having no power to dissolve connective tissue), normal intestinal digestion cannot take place if the connective tissue has been disorganized in the meat. It is therefore, advisable not to give raw meat in gastric ulcer, but to give it after it has been thoroughly cooked and cut up before it is placed in the mouth. As gastric juice is a stimulant to the secretion of gastric juice,<sup>1</sup> it must be given in ulcer, all forms of gastritis with an excessive secretion of gastric juice, in hyperchlorhydria. Of course, the same effect is produced by the extractive substances of the meat. Schmidt's diet, a carbohydrate diet in hyperacidity placed him on a diet which the writer first established experimentally. It consisted of the amount of HCl secreted by the stomach on a consistent carbohydrate diet, provided there is no fermentation.<sup>2</sup> From recent dietetic studies it is known that rest, absolute exclusion of food for period of four to forty-eight hours, is one of the most effective means of resting the stomach from all irritative gastric conditions. The gastric secretion is depressed or arrested. The use of scraped beef and beef extract appears logical in such cases where secretory powers.

The medicinal treatment of gastric ulcer is given in the recent publications on the subject. The foundation of the treatment of gastric ulcer is bismuth combined with alkaline mineral

<sup>1</sup> Pawlow. Die Arbeit der Verdauungsdrüsen.

<sup>2</sup> Beiträge z. Diätotherapie bei Magen- und Duodenalulcer. Wochenschrift, Nos. 6, 7.

<sup>3</sup> Hemmeter. Archiv f. Verdauungs-krankheiten.

<sup>4</sup> Therapie der Gegenwart, No. 11.

10 gm. (75 gr. to 150 gr.) of bismuth subnitrate in water, which the patient drinks, and increases the dose up to 20 gm. (300 gr.). Unfortunately, such doses of bismuth inevitably cause persistent constipation.

This is the objection also to Pariser's treatment.<sup>1</sup> My personal prefer-

based on a large experience, is to neutralize the gastric contents at breakfast by washing it out with a solution of bicarbonate of soda in which 2 drachms of finely divided chalk are suspended. After

the mixture of equal parts of bismuth subnitrate and bismuth subgallate is allowed to run into the stomach through a stomach-tube, 2

ounce of the mixture in 500 c.c. or half a pint of warm water. By

the patient must attempt to get the bismuth over all

the ulcer; it is allowed to remain in the stomach for two or three

days and then siphoned out. No meal is then taken for two

days. A patient subsisting on a Boas rectal enema in the

*Zeitschrift der Gegenwart*, 1902, No. 2, P. Cohnheim

advocates the use of large doses of olive oil in the

treatment of the ulcer. Fleiner<sup>2</sup> also washes the stomach with a 1

per cent solution of nitrate of silver. Ageron<sup>3</sup> and the writer

have obtained good results with a combination of the olive oil and

about half a pint of cottonseed or olive oil are

to 2 drachms of bismuth subgallate and allowed

to run through a stomach-tube. The patient then

assumes the dorsal, and ventral positions in order to spread the

over the entire internal surface of the stomach.

**DURING GASTRIC ULCER.** These are described in the literature. The explanation of this kind of fever is not given.

**TREATMENT OF GASTRIC ULCER** is considered in the literature. The latest

is to be found in *PROGRESSIVE MEDICINE*, June,

**GASTRIC HEMORRHAGE.** In hæmatemesis

<sup>1</sup> results from the subcutaneous injection of epinephrine when other hæmostatic procedures failed. Grunow<sup>6</sup>

<sup>2</sup> have had personal experience with this

<sup>3</sup> sterile gelatin solution warmed to body

temperatures varying from 150 c.c. to 200

c.c. about a pint and a half of blood by hæma-

toxy as to encourage me in the further use of

it.

vol. iv. p. 31.

<sup>1</sup> 1902, Nos. 22-24.

<sup>3</sup> *Ibid.*, No. 30.

No. 10; also, *Wiener med. Presse*, 1902, Nos. 19, 20.

*ibid.* xiii., No. 2.

1902, No. 32.

A case of *parenchymatous gastric hemorrhage* is described by Moser<sup>1</sup> which seemed to be due to chronic hyperplastic gastritis. A large number of operations for gastric ulcers are described in American, English, and German literature of the past twelve months, and the favorable results would indicate that this method of procedure is the correct one; but as it does not belong within the limits of a clinical report, the surgical treatment of this disease must be referred to another section of this work.

**Cancer of the Stomach.** Concerning the etiology of cancer of the stomach, the research of G. Fütterer<sup>2</sup> has been given in *PROGRESSIVE MEDICINE*, 1902, Vol. IV. p. 35. Fütterer describes the development of an adenocarcinoma at the edges of experimental gastric ulcers in rabbits. His research can, therefore, throw light only upon this type of gastric cancer, and not upon the colloid, the cylindrical cell, or the scirrhus carcinoma. How frequently a carcinoma develops on the edges of a gastric ulcer is difficult to determine with accuracy, for this depends upon a searching histological examination of the cancer, and it is regrettable to state that in the reports from operations and autopsies there is rarely a histological examination, and even if there is one it is not undertaken with a view of determining the histogenetic derivation of the cancer. The greatest importance attaches itself to the researches concerning the pathogenesis of gastric cancer, because *the stomach is the organ most frequently affected by cancer*, and because the treatment of this dreadful disease can be advanced only by a better understanding of the nature and cause of malignant neoplasms. In this connection I have emphasized the hopefulness of a study of the cancer problem from the chemical and physical standpoint.<sup>3</sup> While I do not assert to have produced actual adenocarcinoma, my experiments are suggestive because adenomata were produced at the edges of pre-existing gastric ulcers by the injection of a sterile and cell-free extract of a gastric adenocarcinoma from another animal of the same species. The behavior of cancer cells in solution isotonic with the blood cells and of normal cells of the same tissue in cancer juice, the former contracting in solutions isotonic with the blood plasma and the normal cells swelling up in cancer juice, indicate that there are distinct abnormalities in growth depending upon the physical condition inherent in the cell and not necessarily upon an invading micro-organism. I have also pointed out that the serum of cancer patients may contain anticarcinoma substances capable of destroying the carcinoma cells to a large extent, at

<sup>1</sup> Münchener med. Wochenschrift, November 4, 1902.

<sup>2</sup> Journal of the American Medical Association, March 15, 1902.

<sup>3</sup> On the Rôle of Intracellular Catalytic Processes in the Pathogenesis of Malignant Neoplasms. American Journal of the Medical Sciences, April, 1903, p. 666.



least as long as the circulation is not overcrowded with this cellular infection. It is conceivable that the diagnosis of cancer may be made in future by the reaction which the serum of a cancer patient may show in its effect upon the normal cells of a healthy individual. By this I do not refer to the blood cells, but cells from the normal organ corresponding with the one which is diseased in the cancer patient. That all adenomata which grow from the edge of a gastric ulcer are not malignant is evidenced by a case reported by Albu,<sup>1</sup> in which a palpable benign tumor of the stomach was removed by operation. It was a simple glandular hypertrophy developing from an old cicatrix.

BEHAVIOR OF THE CHLORIDES IN THE STOMACH AND THE CAUSE OF THE ABSENCE OF HYDROCHLORIC ACID IN GASTRIC CARCINOMA. Some clinicians believe that in cancer of the stomach less HCl is secreted because the oxyntic or acid-producing cells of peptic ducts are diseased or destroyed by the neoplasm or by the accompanying gastritis; others are of the opinion that HCl is still secreted but is destroyed by substances contained in the carcinomatous stomach. Reissner<sup>2</sup> believes, since free HCl may be absent at a very early stage and can reappear after the removal of the cancer, it must follow that the cause of the absence of the acid is removed with the carcinoma, and that the glandular atrophy is only secondary. Reissner's examinations of cancer patients have, moreover, shown that the total chlorides are relatively high, due to an increase of the combined chlorides. The chlorides found in the stomach are derived from the following sources: 1. The neutral chlorides of food and saliva. 2. The free HCl secreted by the gastric glands and that combined with albumins. 3. The combination of chlorine with ammonia. Reissner believes that the total chlorides are increased because a portion of the secreted HCl is neutralized by an alkali derived from the fluid discharged from the ulcerating surface of the carcinoma, and which in itself possesses a large amount of chlorine. He states that a cancer produces changes in the chemistry of the gastric secretion only after it has ulcerated, and that the free HCl is absent because its actually secreted amount is diminished and the existing quantity has been neutralized by the alkali mentioned. The cause for both is ulceration of the cancer.

The objections to the theory of Reissner and others are very weighty. In the first place, there can be no doubt that the oxyntic cells are seriously damaged and often destroyed in cancer. Second, removal of the cancer by surgical operation does not always restore the secretion of HCl; in fact, it only does so exceptionally. Among the thousands of operations

<sup>1</sup> Deutsche med. Wochenschrift, 1902, No. 48, p. 865.

<sup>2</sup> Zeitschrift f. klin. Medicin, 1902, Band xliv. p. 71.

done for cancer of the stomach reported in literature I know of only four in which the operators claimed that a restoration of the HCl secretion had been observed. These are the cases of Rosenheim, Thiers, Terrier and Hartmann, v. Mikulicz, and Kausch. Boas mentioned that he has also observed the restoration of the HCl secretion. Evidently this restoration must be a very rare occurrence. Third, it is not necessary for a carcinoma to ulcerate in order to destroy the HCl secretion, as Reissner says, for this secretion has been repeatedly found lost where the carcinoma had not yet been broken down. I have personally observed it lost in three cases of scirrhus of the stomach without any visible ulceration. Fourth, there is a form of gastric carcinoma that develops on the basis of a pre-existing ulcer in which the HCl secretion is not only maintained to the end of life, but may even be increased. A theory that attempts to explain the absence of HCl on the basis that an ulcerating carcinoma produces something which neutralizes the secreted HCl should be applicable to all forms of ulcerating carcinoma of the stomach. We do not exactly know why the HCl secretion is maintained in *ulcus carcinomatosum*, but it is probable that the oxyntic cells acquire a stronger resistance and a higher development during the hyperchlorhydria which, as a rule, accompanies the peptic ulcer on the base of which the carcinoma later on develops, and as the peptic ulcer was associated with hyperchlorhydria, it is reasonable to presume that the subsequent *ulcus carcinomatosum* may for a long time be associated with an exaggerated functional activity of the acid-producing cells. Fifth, those that adhere to the hypothesis that the cancer could secrete or contain something which could neutralize or destroy the secreted HCl assume, of course, that the HCl is secreted in the normal amount, for it is part of their hypothesis that the oxyntic cells are not or very slightly diseased, and still capable of functioning. They have entirely overlooked the fact that it would require enormous quantities of an alkaline material to neutralize the HCl secreted, for the amount of HCl calculated on two parts per thousand of 600 c.c. gastric juice would, according to Michael Foster, be 12 grammes of absolute HCl or 36 grammes of strong liquid HCl. I have in 3 cases minced up and extracted the entire gastric carcinoma under aseptic conditions, and found that a carcinoma weighing very nearly 100 grammes could not combine with or neutralize more than 4.5 grammes of liquid HCl. Emerson<sup>1</sup> has found that carcinomatous tissue contains substances which can bind HCl, and that the addition of fresh carcinomatous tissue to an artificial digesting mixture will effect a more rapid combination with the HCl. This ceases when the

<sup>1</sup> Archiv f. klin. Med., Band lxxii. p. 415.

mixture is heated to 100° F. Emerson assumes the presence of a ferment in the carcinoma tissue which can digest albumen in the incubator as well as in the human stomach. In his experiments the possibility is not excluded that the ferment he speaks of may be pepsin, for, as is well known, pepsin is frequently secreted when the HCl secretion is entirely absent. In order to make the conclusion unassailable such digesting mixtures must be made entirely sterile, for the bacterial proteolysis is considerable. That there are autolytic ferments in gastric and other carcinomata there can be no doubt, but that such ferments have marked proteolytic power in the presence of HCl is to my mind not yet clearly proven, and seems irreconcilable with the well-known fact that the proteolytic power of the gastric secretion in carcinoma of the stomach is, as a rule, far below the normal (Hammerschlag, Riegel, Ewald, Boas, Fleiner, and others).

**HÆMATOLOGY IN THE DIAGNOSIS OF CANCER OF THE STOMACH.** Monisset and Tolot<sup>1</sup> studied the blood in eight cases of cancer of the stomach with the Hayem hæmatimeter and the hæmochromometer of Malassez. Their findings are not of decided diagnostic value, for they find that the diminution of the number of red corpuscles is proportionate to the general health of the patient. The ratio of the hæmoglobin percentage to the red corpuscle percentage—that is, the diminution of the globular value—may be a significant sign of cancer in the stomach; but it may be absent owing to the slow development of the lesion. Leucocytosis is a late phenomenon, and does not appear until the period of cachexia, or as a result of intervening inflammatory complications.

In previous reports on the subject significance has been attributed to leucocytosis in its various fluctuations for the diagnosis of gastric cancer, but these observers state that definite deductions from the kind of leucocytosis are not possible. This is in agreement with my own interpretation that not all cases of gastric carcinoma show a leucocytosis and that the digestive leucocytosis is not absent in all cases of gastric cancer.

The surgical treatment of cancer does not properly belong within the limits of this report.

**Stiller's Pathognomonic Sign of Gastropotosis, the Floating Tenth Rib,** has received the careful study of W. Zweig and B. Stiller.<sup>2</sup> The essential deductions are that this sign really is valuable in the diagnosis of nervous dyspepsia. Stiller is also very impressive in defending his original assertion that nervous dyspepsia and enteroptosis

<sup>1</sup> *Revue de médecine*, 1902, p. 844.

<sup>2</sup> *Archiv f. Verdauungs-krankheiten*, Band vii.



are identical in the large majority of cases, and that the tenth rib is floating and not attached to the costal cartilage in the great majority of these cases. I have paid especial attention to this sign, and in the main can confirm Stiller's conclusions. All cases of gastropotosis that I have seen at my clinic and private practice during 1902 had this floating tenth rib. I cannot support the conclusions of Kuttner<sup>1</sup> that a splashing sound at the height of digestion means gastric atony. This sound can be elicited in healthy individuals if the diet contained much liquid. It certainly is not true that splashing sounds elicited a quarter of an hour after drinking a half a pint of liquid signifies a pathological condition of the gastric tonicity, as A. Rosenbaum asserts.<sup>2</sup> Perhaps the most important advances in the treatment of *dilatation* and *gastropotosis* have been made in a surgical direction. Most noteworthy of these advances is the operation by Henry D. Beye.<sup>3</sup> The principle of this operation is considered histologically and surgically ideal. Some cases are reported in which the patients have secured complete relief. My standpoint concerning the necessity of operation for gastropotosis is this: a stomach may be out of place and still digest normally. Among my fifty students, four who were perfectly healthy had gastropotosis, and presented no symptoms. Furthermore, even in those cases which did give rise to symptoms medical treatment is perfectly competent to effect lasting improvement and sometimes a cure; whereas surgical treatment, although cures are conceded to be possible, can by no means confidently guarantee a recovery. A. E. Maylard,<sup>4</sup> in an interesting paper, emphasizes "The Value of Rest as Effected by Operations in Diseases of the Alimentary Canal." While I agree with him concerning the value of operation in gastric ulcer, pyloric stenosis, chronic ulcerative colitis, and dilated colon, I am of the opinion that he goes too far when he advises gastrotomy for hyperchlorhydria and chronic gastritis. These diseases are perfectly curable by purely medical means.

**Neuroses of the Stomach.** Although over three-fourths of all gastric diseases as they present themselves to the practitioner are comprised under the group of "neuroses," very little of value has been published concerning this important class of gastric diseases during the past year. In the preceding I have already emphasized that which is of diagnostic and therapeutic importance concerning the differentiation of gastric diseases with a distinct anatomical substratum and the gastric neuroses without any histological change in

<sup>1</sup> Berliner klin. Wochenschrift, 1902, No. 50.

<sup>2</sup> Deutsche med. Wochenschrift, No. 25.

<sup>3</sup> The Elevation of the Stomach in Gastropotosis by Plication of the Gastrohepatic and Gastrophrenic Ligaments. Philadelphia Medical Journal, February 7, 1903.

<sup>4</sup> Glasgow Medical Journal, November, 1902.



the stomach. In this connection it was emphasized that future researches will more and more demonstrate that some of the neuroses will be found to be associated with definite histological changes in the gastric mucosa. This constitutes one of the difficulties in nomenclature in designating stomach diseases, according to the character and amount of secretion found. From what has been said in the preceding, for instance, it by no means follows that hyperchlorhydria is always associated with excessive proliferation of the oxyntic or acid cells, nor that achylia gastrica is invariably associated with atrophy of the gastric mucosa. The relation between achylia gastrica and pernicious anæmia are discussed by Einhorn,<sup>1</sup> in which he emphasizes that most cases of achylia have nearly a normal condition of the blood. In one case of achylia with total atrophy of the stomach pernicious anæmia did not exist during life. He confirms the observation already made by myself and others that gastric juice may be secreted in typical cases of pernicious anæmia, sometimes even in excessive amount, and he points out that if pernicious anæmia were caused by atrophy of the stomach the achylia would have to be well marked as soon as the symptoms of the blood disease are evident.

**Heterochylia.** In 1897<sup>2</sup> I first pointed out that a rapidly alternating state of gastric secretion may occur in patients afflicted with nervous dyspepsia, whose stomachs were of normal size, in normal condition, and not afflicted by any of the anatomical diseases. These variations may extend from complete achylia to hyperchlorhydria in the same individual after the identical test-meals and under the same conditions. It is important to exclude dilatation and motor insufficiency in such cases. Dr. George Korn,<sup>3</sup> in a research from Boas' laboratory, Berlin, confirms my observation, which had already been confirmed by Frank H. Murdock.<sup>4</sup> I have personally observed cases of achylia gastrica off and on for six years, one case for six years and eight months, in which no trace of free HCl and ferment was found in many quantitative analyses. Finally, a test-meal was drawn which gave a normal or excessive amount of HCl and ferments. It is evident that such cases cannot depend on atrophy of the gastric mucosa. It may be that the oxyntic or border cells are innervated by a different set of fibres from those innervating the chief or central cells; or it may be that both these cells are supplied by both anabolic and catabolic fibres, in the sense of Gaskell, *i. e.*, accelerating and inhibiting fibres; or it may be that the enzyme body which I have discovered in the saliva and which

<sup>1</sup> New York Medical Record, February 28, 1903, p. 321.

<sup>2</sup> Henimeter. Diseases of the Stomach, first edition.

<sup>3</sup> Archiv f. Verdauungs-krankheiten, Band viii. p. 75.

<sup>4</sup> New York Medical Journal, 1900, and Philadelphia Medical Journal, 1900.

seems to be a normal stimulant to the gastric secretion may at times be absent in such patients. This new body is not always present in the saliva and is most constant when there is a good appetite.

**Gastric Lipase, the Fat-splitting Ferment of the Stomach.** Volhard<sup>1</sup> has demonstrated that a fine emulsion of almost neutral egg and milk fat is split up by the secretion of the stomach into fatty acids and glycerin. About 70 per cent. of the fats introduced are split up in this way. Further facts about this ferment are the following: 1. It is contained in a glycerin extract prepared from the gastric mucosa of the pig. 2. When gained from the secreted gastric juice, gastric lipase is more sensitive to alkalis than when lipase is gained from a glycerin extract of gastric mucosa. 3. The former is more resistant to HCl than the latter. 4. The gastric juice containing the active fat-splitting ferment, the glycerin extract its proenzyme of zymogen. 5. The digestion of fat by gastric lipase apparently does not increase proportionately with the chyme, but is performed in irregular intervals. 6. The reaction is incomplete; only a certain percentage of the fat is acted on. 7. In achylia gastrica this ferment is diminished, together with the other ferments in the stomach. 8. High degrees of hyperacidity interfere with the action of gastric lipase.

## DISEASES OF THE INTESTINES.

**Influence of Intestinal on Pancreatic Secretion.** A valuable contribution to the relation between intestinal digestion and the mechanism of pancreatic secretion is published by W. M. Bayliss and E. H. Starling.<sup>2</sup>

Their conclusions are that: 1. The secretion of the pancreatic juice is normally evoked by the entrance of acid chyme into the duodenum, and is proportional to the amount of acid entering (Pawlow). This secretion does not depend upon a nervous reflex, and occurs when all the nervous connections of the intestine are destroyed.

2. The contact of the acid with the epithelial cells of the duodenum causes in them the production of a body (*secretin*), which is absorbed from the walls of the blood current, and is carried to the pancreas, when it acts as a specific stimulus to the pancreatic cells, exciting a secretion of pancreatic juice proportional to the amount of secretin present.

3. This substance (*secretin*) is produced probably by a process of hydrolysis from a precursor present in the cells, which is soluble in water and alkalis, and is not destroyed by boiling alcohol.

<sup>1</sup> Zeitschrift f. klin. Med., Band xliii. p. 397.

<sup>2</sup> Journal of Physiology, September 12, 1902, vol. xxviii. p. 325.

4. Secretin is not a ferment. It withstands boiling in acid, neutral, or alkaline solutions, but is easily destroyed by active pancreatic juice or by oxidizing agents. It is not precipitated from its watery solution by tannic acid or alcohol and ether. It is destroyed by most metallic salts. It is slightly diffusible through parchment paper.

5. The pancreatic juice obtained by secretin injection has no action on proteids until "enterokinase" is added. It acts on starch and to some extent on fats, the action on fats being increased by the addition of succus entericus. It is, in fact, normal pancreatic juice.

6. Secretin rapidly disappears from the tissues, but cannot be detected in any of the secretions. It is apparently not absorbed from the lumen of the intestine.

7. It is not possible to obtain a body resembling secretin from any tissues of the body other than the mucous membrane of the duodenum and jejunum.

8. Secretin solutions from bile salts cause some increase in the secretion of bile. They have no action on any other glands.

9. Acid extracts of the mucous membrane normally contain a body which causes a fall of blood pressure. This body is not secretin, and the latter may be prepared free from the depressor substance by acting on desquamated epithelial cells with acid.

10. There is some evidence of a specific localized action of the vasodilator substances which may be extracted from various tissues.

**Enterokinase, Eukinase, Pancreatokinase.** Succus entericus, as well as the saline extract of duodenal mucous membrane, contains a body called "enterokinase," which was first investigated in Pawlow's laboratory by Chepownikoff.<sup>1</sup> The pancreatic juice, which is obtained by the action of the duodenal secretin discovered by Bayliss and Starling, is inactive upon proteid (boiled white of egg and gelatin) until it has been acted upon by enterokinase. A complicated but admirable interdependence of the pancreatic and duodenal secretions here becomes evident. 1. The contact of the HCl of the gastric chyme with the epithelial cells of the duodenum causes in them the production of a body called "secretin," which is absorbed from the cells by the blood current, is carried to the pancreas, where it acts as a specific stimulus to the secretion of pancreatic juice, which is proportional to the amount of secretin present. 2. This pancreatic juice, however, though active upon boiled starch, is not active upon proteid until enterokinase is added—another product of the duodenal and jejunal mucosa.

Hallion and Carrion<sup>2</sup> have extracted from the duodenal mucous membrane of the pig a yellowish powder which contains the entero-

<sup>1</sup> Thèse de St. Petersburg, 1899.

<sup>2</sup> Bulletin de générale de thérapeutique, 1903, vol. cxlv., No. 2, p. 53.



kinase of Pawlow in very active form. They have called this duodenal extract *eukinase*, and have recommended it in acute and chronic affections of the intestines, either of primary origin or secondary to infectious diseases. In intestinal dystrophia it is also of great value. Pancreato-kinase is a combination of pancreatin and eukinase, which is also claimed to be a powerful intestinal digestant. These substances, it is stated, are acted upon by gastric juice, which hinders their usefulness. In cases of achylia gastrica, where as a consequence of the absence of the secretion of HCl and pepsin the normal physiological stimulants to the secretion of *secretin*, and consequently of pancreatic juice and enterokinase, are lacking, we are confronted with a complication where both the gastric and intestinal digestive process is gravely defective. In such cases the beef and even fats and carbohydrates may appear in the stools undigested. It is here that the restoration of the normal gastric secretion is the most essential aim of the treatment. Sometimes the addition of thirty to sixty drops of dilute HCl is sufficient to start up the formation of secretin if an enteritis is not present at the same time. Should we, however, be confronted with a simultaneous duodenitis or jejunitis, then we will not be able to set up the formation of secretin unless the intestinal mucosa can be restored to a normal condition. In these complications the extracts of the duodenal mucosa, mentioned in this paragraph, constitute the physiological therapeutics. Care should be taken, however, by the examination of the stools, to see whether or not these substances actually improve the digestion.<sup>1</sup> In associated gastric and intestinal catarrh I have found that pancreon actually improved intestinal digestion as controlled by stool examination. It is one of the preparations belonging to the class mentioned above that has the advantage of not being destroyed by the HCl of the gastric juice. The above researches of Bayliss and Starling and those coming from Pawlow's laboratory demonstrate the fallacy of such statements as that made by Edkins,<sup>2</sup> who gravely announced that he was unable to demonstrate experimentally the existence of an intestinal secretion.<sup>3</sup>

Ponomarew<sup>4</sup> has discovered that there is a secretion of Brunner's glands which digests albumin and fibrin when HCl is added.

**Absorption from the Stomach.** The experiments on absorption thus far reported have shown that water is not absorbed from the stomach, and that there exists great variation in the absorption of

<sup>1</sup> Hemmeter. Use and Abuse of Digestive Ferments, Medical News, June 7, 1902.

<sup>2</sup> British Medical Journal, September 13, 1902.

<sup>3</sup> Modern medical literature is full of publications of this sort, announcing the most contradictory discoveries, which, upon critical judgment, are found to be due to some error of technique or faulty deduction.

<sup>4</sup> Zur Physiologie der Brunner'schen Abteilung des Duodenum. Russki Wratsch., No. 46.



such chemical substances as we use for the relief of suffering and cure of disease. *Nothing can be more relevant than the necessity that we should be sure, at every step of our treatment of any case, that the medicine which we give and upon which life may depend is actually absorbed.* I have frequently been called to cases of complication of valvular disease of the heart with gastric dilatation where the symptoms of failure of compensation were due to the fact that the digitalis and strychnine which had been given remained in the dilated stomach and were not absorbed. In all cases of serious heart trouble with chronic gastritis or dilated stomach the digitalis and strychnine should be given hypodermically or by enema into a previously cleansed rectum.

Since the investigations of Meltzer<sup>1</sup> the most valuable researches on gastrointestinal absorption have been made by V. Otto.<sup>2</sup> This experimenter worked over the results of von Mering on several types of animals—guinea-pigs, rabbits, cats, and dogs—and with a number of different chemical substances (iodide of potassium and sodium, sodium salicylate, chloral, strychnine nitrate). The remarkable result was gained that there are considerable differences in the absorption of these individual substances in the same animal, and that the absorption of these substances varies in the different animals experimented upon. For instance, the small molecule of KI is absorbed readily from the gastric mucosa of the herbivora, while the large molecule of strychnine is not absorbed by these stomachs. On the other hand, the gastric mucosa of the carnivora opposes a very considerable resistance to the absorption of the ordinary diffusible molecule of KI and NaI, while it permits the molecule of strychnine nitrate to pass readily. The deduction which we are justified in making therefrom is that we must not judge from the absorbability in the stomach of one substance concerning the absorbability of a different substance, and, secondly, that the power of absorption of one species of animal cannot be applied to another species or to the human being, as von Mering does. Personally I very much regret that neither the experiments of Otto nor any of the others quoted permit of judging whether sodium salicylate is absorbed from the human stomach. By methods which I demonstrated years ago it is possible temporarily to occlude the human duodenum by blowing up a small pear-shaped balloon in it which is introduced by duodenal intubation.<sup>3</sup> In this manner it would be not difficult to test the absorption of various important drugs from the human stomach, and it is here where a field of research of far-reaching importance is open for the brainy investigator. Even concerning the absorption of

<sup>1</sup> Journal of Experimental Medicine, 1896, vol. i.

<sup>2</sup> Archiv f. Verdauungs-krankheiten, 1902, Band viii.

<sup>3</sup> Hemmeter. Diseases of the Intestines, vol. i. p. 234.

the normal products of gastric digestion a great deal of work has yet to be done. In a recent publication by E. Zunz<sup>1</sup> it is stated that of the products of albumen digestion that are formed in the stomach the albumoses are formed very abundantly, the acid albumen less abundantly, and the remote products of digestion, like peptones and peptoids (the latter being precursory stages of amido-acid) are formed in very small quantities. The greatest part of the soluble products is given over to the small intestine, rapidly split up, and absorbed. In the stomach the absorption is rather small. The remote products of digestion are first absorbed—peptones, etc.—then to a less degree the albumoses. The remote products, like peptones and peptoids, are present in the stomach only in small quantities, and, therefore, their absorption has but small significance. The substances which no longer give the biuret reaction are those which are principally absorbed from the stomach. The absorption of albumoses is not excluded, however, because their presence can be demonstrated in the wall of the intestine.

**The Special Pathology of the Intestine.** The special pathology of the intestine will be considered in connection with the diseases concerning which something new of real merit can be reported. But inasmuch as intestinal autointoxication depends on the quantity and quality of the bacteria present, this subject will merit special attention. Klein<sup>2</sup> concludes that nowhere in the normal intestine does an augmentation of the bacteria occur, and that there is no bacterial flora peculiar to the intestines. All bacteria are derived from the food, and the bacteria die off and decrease continually. This destruction of bacteria is strongest in the cæcum, appendix, and ascending colon. The colon bacteria are very resistant, and wherever there is an increase of bacteria this is to be attributed to a reduction in the antibacterial provision of the intestines and a pathological condition. As the bacteria are continually decreasing in number, a continual destruction of them taking place, Klein does not attribute to bacteria a rôle in the digestive act.

**The Permeability of the Juvenile Intestinal Wall for Tubercle Bacilli** has been investigated by Disse,<sup>3</sup> who explains the ability of tubercle bacilli to pass through the intestinal wall in youthful individuals by the fact that the protoplasm of the epithelial cells is not yet covered by a continual stratum of mucus. Only here and there single plugs of mucus project from a protoplasmic network. As the individual grows these plugs extend in breadth. A special tinctorial

<sup>1</sup> Ueber die Verdauung u. Resorption der Eiweisskörper im Magen und Anfangsteil des Dünndarms. Hofmeister's Beiträge zur chem. Phys. und Path., Band iii., Heft 7, 8.

<sup>2</sup> Die physiologische Bacteriologie des Darms beim Kaninchen, Nederlandsch Tydschrift van Geneeskunde, 24.

<sup>3</sup> Berliner klin. Wochenschrift, 1903, No. 1.

method was necessary to demonstrate this. In the *Deutsch. med. Wochenschrift*, September 24, 1903, von Behring uses this same argument to prove that the only source of infection with tubercle bacilli in the human infant is milk of the human mother or tuberculous cows.

**The Bacteriology of Dysentery and Summer Diarrhœa of Children.** There can be no doubt at the present time that dysentery can be caused by a variety of micro-organisms. The amœbic dysentery, first classically described by Kartulis, has been confirmed as occurring in this country by many competent American investigators. After the discovery of the cause of the dysentery, which is epidemic in Japan, by the Japanese bacteriologist, Shiga, Flexner discovered that the same organism is the cause of certain types of this disease in this country. A. J. Lartigan<sup>1</sup> found that the bacillus pyocyaneus was the cause of fifteen cases of dysentery occurring at Hartwick. In 1901 and 1902 I found that the dysentery occurring in two children of one family was due to the "*Lamblia duodenalis*" (Lambl, 1859). Lambl has discovered two organisms which are named after him—one in 1859 and one in 1875.<sup>2</sup> This parasite is a protozoan belonging to the flagellata. In one of my cases the stools were examined by Dr. C. W. Stiles,<sup>3</sup> of the Bureau of Animal Industry, Washington, D. C., who pronounced it the first case of the presence of this parasite in man which has yet been diagnosed in the United States.

Ward<sup>4</sup> describes the case of an American physician who contracted dysentery in the Philippines. The amœba coli and the ova of uncinaria were found in the stools, and both infections were believed to have been simultaneously present from the first. The bacterial flora of forty-two typical cases of summer diarrhœa of infants have been studied by C. W. Duval and V. H. Bassett<sup>5</sup> at the Thomas Wilson Sanitarium of Baltimore. They succeeded in isolating from the stools the bacillus dysenteriae of Shiga. They believe their findings justify the conclusion that the summer diarrhœas of infants are caused by the intestinal infection with the bacillus dysenteriae of Shiga, and, therefore, are etiologically identical with the acute bacillary dysentery of adults.

This last sentence is dangerous from its sweeping generalization. If from what I have said above the forms of dysentery in the adult are unquestionably due to a variety of forms of micro-organisms, the same can be demonstrated to be true of the group of diseases known as the infantile summer diarrhœa. In addition to the fact that the summer

<sup>1</sup> Journal of Experimental Medicine, vol. iii. p. 595.

<sup>2</sup> Hemmeter. Diseases of the Intestines, vol. ii. p. 544.

<sup>3</sup> Washington Medical Annals, March, 1902, vol. i., No. 1, p. 64.

<sup>4</sup> Albany Medical Annals, January, 1903.

<sup>5</sup> American Medicine, September, 1902, p. 417.



diarrhoea of infants may be due to entirely different organisms, some of which belong to the group of protozoa, as, for instance, in my cases, there have been demonstrated such elementary differences in the variety of bacilli found in the intestines of those suffering from acute dysentery that the hope of a serum treatment for dysentery is still very remote.

Martini and Lentz assert that the Shiga type of dysentery bacillus differs from Flexner's Manila-Baltimore type in cultural and agglutination reaction; and Park and Carey<sup>1</sup> suggest that in Japan, as well as in America and elsewhere, there is not only one, but several varieties of this group of bacillus dysenteriae of Shiga. In the United States the more accurate agglutination tests and new culture media have brought to light the fact that in different epidemics the bacilli believed to have excited the disease vary so greatly from the original culture of Shiga that at present it is impossible to decide whether a single group can comprise all these varieties; and in my opinion it will be as yet impossible to predict whether the bactericidal properties obtained through the injection of animals with one type of culture can produce a serum which will cure the dysentery in persons suffering from another type. All this should caution us to be conservative with regard to the promises of a curative serum treatment for dysentery.

**Gastrointestinal Autointoxication.** The most comprehensive treatment of this subject in American literature has been given by myself.<sup>2</sup>

Ravenna succeeded in demonstrating experimentally that degenerative changes could be produced in the ganglia of the plexus of Meisner and Auerbach, with increase of the connective tissue, by introducing certain toxins into the intestines of guinea-pigs and rabbits. Even in the human being these changes could be demonstrated, and were more evident after acute than after chronic enteritis.<sup>3</sup>

**THE ORIGIN AND DEVELOPMENT OF THE ETHEREAL SULPHATES.** Sulphuric acid occurs in the urine in two forms: (1) the preformed sulphates, and (2) the ethereal sulphates. The ethereal sulphates have, since the important researches of Baumann and Herter,<sup>4</sup> been looked upon as an important criterion of the degree of intestinal putrefaction. The presence of the conjugate sulphates in the urine has gained important physiological and toxicological significance by the work of Baumann, showing that the formation of phenol-sulphuric acid is an expression of an antitoxic influence of the organism in rendering the

<sup>1</sup> Journal of Medical Research, March, 1903, p. 189.

<sup>2</sup> International Clinics, 12th series, vol. i. pp. 107-126, and vol. ii. pp. 155-176.

<sup>3</sup> Sulla patologia dei plessi nervosi del intestino. Arch. per le scienze méd. del Bizzozzero.

<sup>4</sup> Zeitschrift f. physik. Chem., Band i. p. 244.



phenol less poisonous—phenol being a substance which is formed in the intestinal canal as a result of putrefaction of proteid substances, and is excreted in the form of an ethereal sulphate, together with numerous other substances of a toxic nature which are combined with sulphuric acid in a similar way before their excretion.

As far as our efforts at intestinal asepsis are concerned, it was important to know whether the ethereal sulphates are formed in the intestine or in another organ, for if they are to serve as an index of intestinal putrefaction this question is very important. Numerous investigators have attempted a solution of it, and the most recent is by Gustav Embden and Karl Glaessner.<sup>1</sup> They arrive at the conclusion that the liver is by far the most important organ concerned in the formation of the ethereal sulphates. Small amounts of ethereal sulphates are also formed in the kidneys and lungs. They failed to demonstrate that the intestine produces ethereal sulphates.

**The Influence of Antiseptics in the Quantity of Bacteria in the Intestines.** J. Strasburger<sup>2</sup> has found by clinical observation and animal experimentation that it is useless to attempt intestinal antiseptics by the administration of drugs. A slight decrease in bacterial growth may at first occur, especially in the small intestine; but this is soon followed by an increase, owing to interference with the natural protective powers of the bowel. The bacteria in the bowel are for several reasons necessary for the well-being of the organism, and a rational antiseptics should have in view the holding of the number and kind of bacteria within normal bounds. Purgatives are the most effective antiseptics, as they remove the culture media upon which the bacteria flourish. But even here there is a danger of interfering with normal functions, as is shown by an increase in the bacteria some time after their administration. The best way to accomplish a practical intestinal antiseptics is by producing a normal condition of the intestines themselves and by administering food that is easily and rapidly digested.<sup>3</sup>

It is impossible to abstract such a long article as that by myself within the limits of this report, but our main hope for the future lies not in intestinal antiseptics, but in lavage of the stomach and colon and increasing elimination through the kidneys and skin. I do not wish to imply that the so-called intestinal antiseptics are absolutely useless, for it has been found by R. Stern,<sup>4</sup> in disinfection of the intestinal canal, that the bacteria which are passed out after the use of calomel, for instance, die within twenty-four hours after the passage of the stool, and

<sup>1</sup> Hofmeister's Beiträge zur chem. u. physik. Pathologie, Band i. p. 310.

<sup>2</sup> Zeitschrift f. klin. Med., Band xlviii. p. 491.

<sup>3</sup> International Clinics, twelfth series, vols. i. and ii.

<sup>4</sup> Zeitschrift f. Hygiene, Band xii.

Mieczkowski found that after large doses of menthol the chyme flowing out of a fistula of the small intestine could no longer be used as a culture media for intestinal bacteria.

**Effects of Resection of the Intestine.** In connection with the large parts of the human intestine which are from time to time reported as having been removed surgically, the following investigation is of importance. Joseph Erlanger and Albion Walter Hewlett,<sup>1</sup> from "A Study of Metabolism in Dogs with Shortened Small Intestines," conclude that:

1. Dogs from which from 70 to 83 per cent. of the combined jejunum and ileum have been removed may live indefinitely after recovery from the operation. Their nutrition may appear to be perfectly normal, or it may be so poor that even when eating ravenously they do not appear to be able to keep well nourished.

2. Such dogs are peculiarly liable to be affected with diarrhœa, which may be caused by a diet too rich in fat or one containing too much inert, non-digestible material. This diarrhœa is of very serious moment to such a dog, and may cause its death.

3. The urine of such dogs shows no great variation in quantity, specific gravity, or nitrogenous contents from that of normal animals.

4. The conjugate sulphates in the urine are increased absolutely and relatively to the alkaline sulphates, indicating an excess of intestinal putrefaction.

5. The quantity of fæces varied in their two animals. In the dog from which 70 per cent. of the movable small intestine had been removed there was no marked increase in the amount of fæces; in the dog from which 82 per cent. had been removed the amount of fæces was increased.

6. The percentage of water in the fæces of dogs deprived of large amounts of small intestine may equal or only slightly exceed the percentage of water in the fæces of normal dogs. This is in contrast with the increased percentage of water in the fæces of animals deprived of the large intestine.

7. On a diet poor in fat the dog with the shortened small intestine absorbs the fat as well or almost as well as a normal dog. As the fat in the diet is increased the fall in the percentage eliminated in the fæces which occurs in the normal animal may either occur to a less extent or may not occur at all in dogs deprived of small intestine. With large amounts of fat in the diet 25 per cent. of that ingested may appear in the fæces, whereas in their normal dog only about 4.5 per cent. appeared.

<sup>1</sup> American Journal of Physiology, September 1, 1901, vol. vi. p. 26.

8. The addition of fat to the diet of a normal dog does not greatly affect the amount of nitrogenous material eliminated by the feces. The addition of fat to the diet of dogs deprived of small intestine causes an increased elimination of nitrogenous material in the feces. On a diet rich in fat the amount of nitrogen eliminated in the feces may be double that eliminated by a normal dog, although on a diet poor in fat there is no great difference between the two.

These experiments of Erlanger and Hewlett confirm my observations on human beings who had been subjected to the necessity of the excision of a large part of their intestine, and as a consequence of defective utilization of the food they are very much more prone to infectious diseases than people with the normal length of intestine. A person deprived of from five to six feet of his intestine is, in my opinion, as much maimed and more hopeless in the struggle for existence than a cripple after a hip-joint amputation.

**Meteorism and Intestinal Atony.** Van Noorden recommends physostigmine in doses of 0.0005 to 0.0007, three to four times daily, in the form of a powder with milk-sugar. The undesirable collateral effects he combats with small doses of atropine.

**Sigmoiditis.** Following the recognition of this localized inflammation of the sigmoid flexure which was given by Mayor, and two cases observed by myself,<sup>1</sup> Bittorf<sup>2</sup> describes two cases of inflammation of the sigmoid flexure due to *coprostasis*, and Messedaglia<sup>3</sup> gives a literary compilation of all cases of this kind thus far reported. In one of Messedaglia's cases the inflammation had started from a rectal fistula. All of these cases may lead to perisigmoid abscesses and perforation. The treatment must be directed to keeping the sigmoid flexure clean by liquid diet and castor oil, irrigations with solutions of tannic acid, and absolute rest in bed. The principal symptoms are a cylindrical resistance sensitive to pressure in the left iliac region, meteorism, fever, alteration of the general condition, and sometimes sigmoid volvulus. The diagnosis must exclude tumors, paranephritic abscesses, perityphlitis, and pericolitis.

**Neoplasms and Tumors.** W. R. Stokes<sup>4</sup> and myself have described a case of chronic hypertrophic gastritis of syphilitic origin. Two similar cases have since been reported, one by Müller<sup>5</sup> and the other by Heinrich Gross.<sup>6</sup> These cases are important not only as neoplasms, but also as causes of gastric and intestinal strictures.

<sup>1</sup> Hemmeter. Diseases of the Intestines, vol. i. p. 505.

<sup>2</sup> Berliner klin. Wochenschrift, 1903, No. 7.

<sup>3</sup> Il Morgagni, part i., H. 6, p. 375.

<sup>4</sup> Archiv f. Verdauungs, Band vii. S. 4, 5.

<sup>5</sup> Wiener klin. Rundschau, 1902, No. 12.

<sup>6</sup> Münchener med. Wochenschrift, 1903, No. 1.



**Intestinal Occlusion due to Cholelithiasis.** The diagnosis of intestinal obstruction is a serious matter to the general practitioner in those cases in which the intestinal obstruction is a result of a precursory condition which generally falls under the observation of the practitioner. During the past year (1902 to 1903) I have had five cases of duodenal and jejunal obstruction which were the direct result of cholelithiasis. In four of these cases the diagnosis of cholelithiasis was established before the operation. All four had dilated stomachs, with a fairly normal or excessive secretion of HCl. In two the enlarged gall-bladder and perieystic inflammation were palpable. The operations were performed in one case by John B. Deaver; two by L. McLane Tiffany; one by J. M. T. Finney, and one by Randolph Winslow. In all of these cases the normal function of the intestine was restored and recovery perfect. In one case—that operated on by Finney—the gallstones had perforated the gall-bladder, and twelve of them were found lying in a space surrounded by peritonitic adhesions, some of which extended around the duodenum about an inch below the pylorus. In another case—that operated on by Winslow—the entire gall-bladder had become cirrhotic, and had tightly contracted around a gallstone the size of a small marble. There were also adhesions extending to the duodenum, and stones in the common duct. The case operated on by Deaver I did not see at the operation, and do not know the particulars. In addition to these five cases I have a record of five others which were operated on in previous years in which adhesions primarily due to cholecystitis and cholelithiasis caused duodenal and jejunal strangulation by adhesions. J. Bodganik<sup>1</sup> reports two cases of intestinal occlusion associated with cholelithiasis in which the symptoms of this latter disease were not evident, but alarming symptoms of acute occlusion called for immediate laparotomy. All such cases demonstrate the wisdom of early operation in all cases of intestinal occlusion, whether the cause is known or not, and, furthermore, that all cases of gallstone disease should be advised to consent to operation as a matter of principle, just as we advise operation for purulent appendicitis. In only two out of the five cases of occlusion due to cholelithiasis was there a distinct history of previous jaundice, which confirms the assertion of Hans Kehr that jaundice is a rather rare occurrence in connection with this disease.

In the section devoted to the diseases of the liver I shall return to a consideration of this subject.

**Colica Mucosa; Mucous Colic of the Intestine.** Van Noorden and Dapper assert that the condition is chiefly a neurosis of secretion, and

<sup>1</sup> Wiener med. Presse, No. 45.



this justifies them in rejecting the safe bland diet and advising a stimulating and brusque diet, with considerable dietetic ballast, in order to combat the constipation which they conceive to be the main cause of colica mucosa. They also recommend oil clysters, massage, and mineral waters. In criticism of this monograph of Van Noorden I have to call attention to the fact that while there is a colica mucosa which is not associated with any anatomical changes in the colon, there is undoubtedly also a *colitis membranacea* which is associated with anatomical changes and clinically very difficult to distinguish from the purely neurotic form which these authors describe, and the treatment advised by them would, if applied to the colitis membranacea, actually do harm in my opinion. Personally I would recommend trying the bland diet first. For instance, a diet consisting of rice, sago, farina, strained oatmeal, chocolate, white bread, egg albumen and gelatin, and a small amount of good wine, gradually passing over to a diet of scraped meat, bread and butter. Milk should be excluded until improvement is very evident.

**Enteroptosis; Gastropptosis.** The various hypotheses concerning this condition, the methods of diagnosis and treatment, have recently been ably recapitulated in American literature by J. Dutton Steele<sup>1</sup> and Albert P. Francine.<sup>2</sup> The deductions of both of these writers are based on considerable experience, and while they present nothing new it is a comfort to realize that we are more and more approaching clearly established principles in diagnosis and treatment. J. Dutton Steele emphasizes that the treatment must chiefly be directed to securing rest for the stomach. This is best accomplished by allowing only small amounts of food at a time, and by making sure that the stomach has a period of rest between the meals in which it is absolutely free of food. This can only be ascertained, of course, by repeated examinations with the stomach-tube. If the stomach is not entirely empty after five hours after a meal we must allow six hours, and so on. The operation for restoring a displaced stomach, as first suggested by Beyea and employed in a case of Stengel's, has been described in the preceding text. The operation consists in shortening the gastrohepatic omentum by a series of ligatures. Since the publication of the article by Stengel and Beyea,<sup>3</sup> Blecher<sup>4</sup> has reported four cases of gastropptosis and one of enteroptosis which were treated by a similar operation by Bier, with very satisfac-

<sup>1</sup> Gastropptosis and Gastric Motor Insufficiency. Philadelphia Medical Journal, January 25, 1902.

<sup>2</sup> Gastropptosis: A Critical and Clinical Study, with Reference to 100 Cases, Philadelphia Medical Journal, January 3, 1903.

<sup>3</sup> Transactions of the College of Physicians, vol. xxi.

<sup>4</sup> Deutsche Archiv f. Chirurgie, 1900.

tory results. Webster has recently recommended an operation which seeks to restore the tonicity of the abdominal recti muscles by excising that portion of the connective tissue lying between the recti and thereafter stitching the muscles together. A strip of skin and fat is cut away from the side of the wound before it is closed. It is noteworthy to emphasize that both Blecher and Webster insist on prolonged after-treatment of rest and massage and abdominal support, and Blecher urges that an operation is only desirable when a prolonged rest cure and the use of an abdominal support have proved to be of no benefit, when the ptosis is extreme, or when the patient is unable to afford the time and money for more conservative treatment.

In a very extensive personal experience I have found the diet and rest cure with abdominal support sufficient in the great majority of cases of gastropptosis; massage and electricity and hydrotherapeutics, together with tonic medication, are generally indispensable. I do not mean to assert that permanent restoration of the stomach to its normal position may occur by non-operative measures, but I do believe that the comfort of the patient and comparative normal function of the stomach and intestines can be immeasurably increased by non-operative treatment.

This is not the proper place to speak of the many devices for supporting the abdomen, but it will do no harm to again emphasize the necessity for restoring the support to the pelvic floor in women suffering from enteroptosis. Abdominal support and restoring the recti will do little good when the uterus and adnexa can be displaced into the lower pelvis by the external abdominal pressure. The after-treatment of pregnancy must also be here referred to, nor will it be considered redundant to refer once more to the excellent work of Stiller in placing the pathogenesis of enteroptosis in a new light and showing its relations to a *universal congenital asthenia*, the pathognomonic stigma of which is the floating or movable tenth rib. Stiller's work is, in fact, epoch-making, and tends to bring all those disturbances of digestive function which we call "atony" under the diagnostic restrictions of ptosis and the dilatations which may result therefrom. The more I study Stiller's publications and his doctrines on enteroptosis, the more I am impressed with the force of his logic and the correctness of his conclusions. The floating tenth rib, in my experience, occurs in four-fifths of all cases of enteroptosis and gastropptosis. Of course, it is very important to know whether the tenth rib cannot be normally floating, and what the real anatomical connections of the tenth rib are with the costal arch. This subject has been very carefully studied by Stiller on the reports of well-known anatomists, and there is no doubt that the tenth rib in healthy individuals is strongly and immovably fixed to the

costal arch. Stiller<sup>1</sup> has recently replied to his critics, particularly Zweig, with irresistible logic.

**Appendicitis.** There is no medical literature in the world which has handled this subject with greater precision and clearness than American medical literature. The pathogenesis, diagnosis, and treatment of appendicitis have been thoroughly considered in previous numbers of *PROGRESSIVE MEDICINE*. Perhaps one of the most exhaustive articles in American literature, published in 1902, is that by myself.<sup>2</sup> Incidentally I might call attention to the article on "Intestinal Occlusion" in the same work, which brings up the entire literature of the subject to 1902, and in 322 pages represents the most complete recent contribution to that subject of American origin.

The recent literature of genuine interest is not very abundant. A very curious relation between abscess of the tonsil and appendicitis has been reported by Hans Weber.<sup>3</sup> There were three cases of angina tonsillaris immediately followed by acute appendicitis, and Weber conceives that the infected material was swallowed, and, reaching the appendix, there set up an inflammation. Similar cases have been reported previously. Such instances demonstrate that the cause of appendicitis must not always be sought in purely local changes, but that remote infectious and also general infections of the organism may involve the appendix. Thus, we find appendicitis in measles, influenza, parotitis, pyæmia, and even in infections by pneumococci. Sevestre and also Achard and Bracca have reported cases of appendicitis in which the pus contained pneumococci, and in a recent publication Ferrier<sup>4</sup> describes the case of a man, aged twenty-two years, who began with a right-sided pneumonia, later on diarrhœa, and pains under the right costal border. The patient died. The autopsy revealed the appendix enlarged to the thickness of the thumb, freely movable, surface smooth, containing in its interior two or three coffeespoonfuls of creamy pus. On the mitral valve there was a fresh endocarditis; from the pus of the appendix pneumococci and the colon bacillus were cultivated.

**Intestinal Indigestion; Dystripsyia.** This complex pathological condition has recently been worked over by myself.<sup>5</sup> In the same number of the *Medical News* E. Franklin Smith<sup>6</sup> has reviewed some of the etiological factors in intestinal dystripsyia, in which he adopts my

<sup>1</sup> Archiv f. Verdauungs-krankheiten, Band vii. p. 275.

<sup>2</sup> Hemmeter. Diseases of the Intestines, vol. ii. pp. 1 to 86, with illustrations.

<sup>3</sup> Münchener med. Wochenschrift, 1902, No. 52.

<sup>4</sup> Bulletin et mém. de la soc. méd. des hôp., No. 28.

<sup>5</sup> Hemmeter. Intestinal Indigestion (Dystripsyia). Address before the New York Academy of Medicine, December 16, 1902. *Medical News*, April 18, 1903.

<sup>6</sup> Loc. cit., p. 727.



classification. That abnormal processes of digestion can occur within the intestine without any coexistent pathological changes is the chief argument of these papers, but it must be emphasized that they may lead to anatomical changes if the dystrypsia continues.

By intestinal dystrypsia<sup>1</sup> I prefer that the word dystrypsia should be limited to those abnormal forms of intestinal indigestion not associated with actual enteritis or any organic changes, but in which there is chiefly an abnormal fermentation of the carbohydrates, an insufficient digestion of the starches. That these changes are frequent in persons of a neurotic nature has been pointed out by Schmidt and Strasberger.<sup>2</sup> The main object of the treatment is to restrict or exclude these starchy foods, favor evacuation and cleansing of the intestine, for which I prefer two methods, either singly or both together, namely, the time-honored calomel by the mouth or high colon irrigations. The latter can, of course, not influence the abnormal processes in the small intestine, but only prevent the ensuing changes in the colon.

**Intestinal Parasites.** This subject has already been to some extent dwelt upon in the paragraph devoted to dysentery.

**EOSINOPHILIA AND INTESTINAL WORMS.** Lannois and Weil<sup>3</sup> describe a case of *epidermic cysticercus* in which the eosinophilia was reduced after removal of the parasite. A similar reduction of the number of eosinophiles was effected by the injection of extract of male fern. They assert, however, that eosinophilia is an inconstant sign in the presence of *hydatid cysts*. The presence of eosinophilia supports the diagnosis, but its absence does not contraindicate it. The experimental production of eosinophilia by the injection of the contents of a hydatid cyst, or the inoculation with ground-up tapeworms, did not succeed; but Aehard and Loeper brought on eosinophilia by injecting the liquid of an echinococcus cyst into a mouse. Evidently a number of widely different factors are necessary to produce eosinophilia under such conditions, prominent of which are the special idiosyncrasy of the host and the virulence of the parasites employed for the purpose.

Aehard mentions that he has successfully treated hydatid cysts of the liver by injections of extract of male fern. In one case of hepatic cyst no tumor was palpable after three months.

<sup>1</sup> I have first suggested the name of *intestinal dystrypsia* for this condition, because intestinal "dyspepsia" cannot be considered the proper designation, inasmuch as pepsin is physiologically not active in the intestine. The original orthologic derivation of the word "pepsin," coming from the Greek word *πεπτεω*, to digest, also to cook, cannot weaken my claim of the urgency of the new term "dystrypsia," for at present we do not associate the word "pepsin" with its old Greek meaning, but we understand by this word a definite and well-known ferment formed in the stomach.

<sup>2</sup> Die Fäces des Menschen, S. 186.

<sup>3</sup> Bulletin et mém. de la soc. méd. hôp., No. 32.



BALANTIDIUM COLI AS A CAUSE OF INTESTINAL INFECTION. W. Klimenko<sup>1</sup> reports severe intestinal infections with this organism, the symptoms resembling dysentery. The balantidium<sup>2</sup> is taken into the intestinal canal in pork. Anatomically it causes a condition resembling ulcerative colitis. The mortality of these infections is given as 17 per cent.

PREVALENCE AND GEOGRAPHICAL DISTRIBUTION OF HOOKWORM DISEASE (UNCINARIASIS OR ANKYLOSTOMIASIS). Charles Wardell Stiles,<sup>3</sup> in a scholarly monograph of 121 pages, treats exhaustively of intestinal infection with the hookworm, the morphology, mode of infection with uncinaria, the diagnosis, and treatment. It is of importance to know that uncinariasis is of frequent occurrence in the United States. Stiles has pointed out that we have in this country a form of the disease which is due to a special variety of the parasite, the uncinaria Americana.<sup>4</sup> Concerning the methods of diagnosis no special technique is necessary. A small amount of feces are taken from near the surface of the mass, about the size of the head of a large pin. This is spread out in a drop of water on a large two by three-inch slide, which is more easily manipulated by the ordinary size of slide, and is much cleaner to handle. The examination is made with a Zeiss 8 mm., Zeiss C, or a Bausch & Lomb one-third inch. It is not well to use too strong an illumination, and we should look carefully for an elongate oval egg with thin shell and with protoplasm either unsegmented or in the early stages of segmentation. The older the feces and the warmer the weather, the more advanced will be the segmentation. In case of infection with uncinaria Americana the fully developed embryo may be found within the egg-shell. We must be careful not to mistake for the eggs of the uncinaria the eggs of *ascaris lumbricoides*, which have a thick, gelatinous, often mammillated covering and an unsegmented protoplasm, or the eggs of *oxyuris vermicularis*, with a thin, asymmetrical shell (one side being almost straight) and containing an embryo, or the eggs of *whipworms* (*trichuris trichura*, more commonly known as *trichocephalus dispar*), possessing a smooth, thick shell, apparently perforated at each pole, and an unsegmented protoplasm.

METHOD OF WASHING AND SEDIMENTING FECES. Take one or two ounces of feces, fresh or dry, mix with water, and place in a large bottle, retort, jar, or any other receptacle; add enough water to form

<sup>1</sup> Ziegler's Beiträge zur path. Anat. u. Allg. Path., Band xxxiii. S. 281.

<sup>2</sup> For illustrations of balantidium coli and further particulars, see Hemmeter's Diseases of the Intestines, vol. ii. p. 545.

<sup>3</sup> Report of Public Health and Marine Hospital Service of the United States, Bulletin No. 10, published February, 1903.

<sup>4</sup> First reported to the annual session of the American Gastro-enteriologic Association, Washington, May, 1902.

a pint to two quarts, according to the amount of fæces; shake or stir thoroughly and allow to settle; pour off the floating matter and the water down to near the sediment; repeat the washing and settling several times, or as long as any matter will float. The last time this is done use a bottle or graduate with a smaller diameter, and when the material is thoroughly settled examine the fine sediment. It will be found that the eggs have settled more numerous in the fine sediment than in the coarse material.

In case an unusual amount of large, coarse material is present in the fæces, it is sometimes convenient to pour the entire mass through a sieve, rejecting the portion left in the sieve; or, to wash the fæces in a sieve, holding the latter under water. As a rule, however, the sieve is not very useful in fecal examinations.

The centrifuge does not appear to be of any special value in fecal examinations.

THE BLOTTING-PAPER TEST WITH FÆCES. For persons who are not in a position to make a microscopic examination the blotting-paper test will be found very useful. To make the test use only fresh fæces. Place an ounce or more of the stool on a piece of white blotting-paper (any absorbent white paper will answer the purpose); allow to stand for twenty to sixty minutes; remove the fæces, and examine the color of the stain. In about four out of five cases of medium or severe uncinariasis the stain is reddish-brown and immediately reminds one of a blood stain. In making this test on anæmic patients hemorrhoids should, of course, be excluded.

THE TREATMENT OF UNCINARIASIS is by thymol and extract of male fern. Calomel is occasionally advocated.

LOOSS' THEORY OF CUTANEOUS INFECTION WITH UNCINARIASIS. Looss<sup>1</sup> in these publications advanced the startling opinion that the embryos of *ankylostoma doudenale* when placed upon the skin in a drop of water enter the hair-follicles, and from there they seem to bore into the surrounding tissues. Further on they reach the intestines, and there develop into the full parasite. F. M. Sandwith confirmed these observations of Looss, detailing an experiment in which a mixture of charcoal and fæces in which the hookworm larvæ had been bred was smeared on the back of a puppy. Between nine and ten days after the puppy died, and was found to have anæmia in most of his organs, and a plentiful supply of young uncinaria were found in his

<sup>1</sup> Ueber das Eindringen der Ankylostomalärven in die menschliche Haut (Centralblatt f. Bakteriologie, Parasitenkunde, etc., Jena, 1. Abt., v. 29 (18), 31. Mai, 1901, pp. 733-739, 1 pl., Figs. 1-3), and Weiteres über die Einwanderung der Ankylostomen von der Haut aus (Centralblatt f. Bakteriologie, Parasitenkunde, etc., Jena, 1. Abt., v. 33 (5), 6. Feb., 1903. Originale, pp. 330-343 (MS. dated December, 1902)).

jejunum. A second puppy was treated in a similar way, and also died between the ninth and tenth day, the post-mortem showing the same results. The objection to these experiments is that the puppies may have licked up the fecal smear from their back, and that the uncinaria entered the gastric intestinal canal through swallowing. This objection is, however, satisfied by the experiment upon a man, who offered himself to be treated in a similar way upon his forearm, and in his case the first hookworm egg was discovered in his feces on the seventy-first day. In all three experiments the feces were regularly examined for some weeks prior to the experiments, so that the results must be accepted, although they are very startling.<sup>1</sup> A large amount of further experimental material, especially narrating the experiments of Bentley, that the so-called "ground-itch," a form of water sore or affection of the skin confined to the lower extremities, is probably always associated with the larvæ of uncinaria, will be found in the report by C. W. Stiles, above cited. The prophylaxis, therefore, of uncinariasis should take in the disinfection of all skin lesions by carbolic acid or bichloride of mercury, and subsequent protective covering.

**STRONGYLOIDES INTESTINALIS IN THE UNITED STATES.** After a history of this intestinal infection as it occurs in other countries, Price<sup>2</sup> gives the life-history of the parasite and reports a case coming under his own observation. In the discussion on this paper three other physicians reported having observed intestinal affections with this parasite. This shows it to be a more common infection in the United States than was hitherto believed.

**CLINICAL DIAGNOSIS OF INTESTINAL PARASITES.** At the same meeting C. W. Stiles insisted that in all persistent cases of intestinal disease the stools should be regularly examined as long as there was any doubt in the diagnosis. His methods for examining the stools for parasites and their ova have already been stated in the preceding text, and consist mainly in agitating part of the feces with water in a glass jar, then allowing to stand for a short time, and finally the upper liquid poured off. All intestinal parasites sink in water, and can be easily found in the sediment after repeated washing.

**Dietetics and Therapy.** **METABOLISM ON ORDINARY AND FORCED DIETS IN NORMAL INDIVIDUALS.** In a study of this subject Francis W. Goodbody, Noel D. Bardswell, and J. E. Chapman<sup>3</sup> present the following conclusions:

<sup>1</sup> F. M. Sandwith. Proof that *Ankylostoma* Larvæ Can Enter the Skin. *Journal of Tropical Medicine*, London, December 15, 1902, p. 380.

<sup>2</sup> Paper read for the Section on Practice of Medicine, American Medical Association, New Orleans, La., May 5, 1903.

<sup>3</sup> *Journal of Physiology*, July 21, 1902, vol. xxviii., No. 4, p. 257.



1. The lasting bad effects of an excessive diet on normal individuals.
2. The very small quantity of nitrogen retained except when extreme forced feeding is employed.
3. The increased quantity of urine passed and very high specific gravity, more or less proportional to the intake of fluids, this being contrary to what has been observed in pathological conditions.
4. The marked increase in the quantity of total nitrogen in the urine of forced feeding, the proportion of this substance passed as urea remaining normal all through, and there being no marked difference in the proportion of uric acid and ammonia, although there was a slight tendency to increase in the quantity of nitrogen, rest on forced feeding.
5. The marked increase in the inorganic constituents of the urine analyzed for during the period of forced feeding.
6. The fact that, contrary to what was to be expected, there was no marked increase in the total quantity of nitrogen in the fæces on the forced feeding except in Case III., while, as a rule, there was an enormous increase in the total of fats.
7. The temporary increase in the rate of absorption of nitrogen on forced feeding as against the tendency to diminution in the rate of absorption of fats during the same period.
8. The very rapid increase in weight during the period of forced feeding and the very striking rapidity with which this increase disappeared.
9. The marked deterioration in health caused by forced feeding.

**Gastric and Intestinal Crises.** This was the title of an address to the German Medical Society of New York by Prof. C. A. Ewald, of Berlin. Ewald discussed these phenomena as they arose, and were traceable to a lesion of functional disturbance of the kidneys, liver, uterine and ovarian troubles, parasites, autointoxication.

Only in a small degree did he believe them to be the expression of disease of the stomach and intestine. He described the early manifestation of *tabes dorsalis*; the crises return at shorter and shorter intervals, and they last from one-half to forty-eight hours. He admitted that we were ignorant as to the nature of the crises, but favored the view that they were due to an autointoxication by a toxin which could only influence abnormal nerves, the attacks increasing in severity as the degeneration progresses. In grave cases morphine must be given. Ewald has no faith in the efficacy of cerium oxalate, but believes that great comfort can be obtained by epidural injections of cocaine.

## DISEASES OF THE LIVER.

**Icterus.** Concerning the etiology of icterus, in association with *hypertrophic cirrhosis*, Gérardel reports the microscopic examination of



two cases of hypertrophic cirrhosis from which he seeks to demonstrate that the name of *biliary cirrhosis* (Charcot and Hanot) is a misnomer.<sup>1</sup> As is well known, we may make a distinction clinically and pathologically between two essentially different forms of hepatic cirrhosis. 1. One is called the *Laennec cirrhosis*, which is a granular chronic interstitial hepatitis, in the great majority of cases due to alcoholism. This form must carefully be distinguished from the syphilitic, malarial biliary cirrhosis and that due to passive venous congestion. 2. The second form of liver cirrhosis has frequently been called the biliary form, of which there are two sub-varieties: (*a*) the cirrhosis due to the stagnation of bile caused by gallstones, and (*b*) the so-called hypertrophic biliary cirrhosis (*cirrhose hypertrophique avec ictère chronique*), a designation original with Charcot and Hanot. It is this form of cirrhosis with considerable enlargement of the liver, chronic and intense icterus, an enlarged spleen, without ascites, the pathogenesis of which is still obscure. It has nothing to do with alcoholic abuse, and constitutes a disease peculiar to itself. Charcot and Hanot selected the name "biliary cirrhosis," on the assumption that it was due to inflammatory lesions of the bile capillaries, and it is this assumption which Gérardel contests, for he found in his two cases that the bile capillaries were perfectly intact, their cells easily stainable and well defined. The liver parenchyma was studded with numerous nodular accumulations of cells, which contained masses of mononuclear cells within a connective-tissue meshwork. These nodules also contained veins and capillaries. Although the icterus had existed for years in his patients, there was no trace of pericholangitis.

This research suggests that icterus is not due to disease of the excretory elements, but to some abnormality in the secretory function or metabolism in the liver cells.

UROLOGY OF ICTERUS. Referring to the preceding section of hepatic insufficiency and the difficulty in forming an estimate of this condition from the urinary signs, the researches of S. Simnitzki and P. Rodoslawow<sup>2</sup> are of importance as proving that in catarrhal icterus as well as in hypertrophic cirrhosis of the liver a sufficient quantity of urea and phosphates is secreted, and that this quantity may at times exceed the normal. The relative quantity of phosphoric acid secreted is very close to the normal; the amount of the chlorides of the urine is more frequently reduced. The excretion of the extractive substances is increased, and the quantity of uric acid is only slightly increased. The relative amount of the ethereal sulphates shows no or very slight

<sup>1</sup> Comptes rendus de la société de biologie, No. 37.

<sup>2</sup> Centralblatt f. Stoffwechsel und Verdauungs-krankheiten, Erstes März-Heft, 1903, No. 5.

changes. The oxidation processes are lower than under normal conditions.

**CHRONIC CONGENITAL ICTERUS.** Widal and Ravaut<sup>1</sup> presented a patient, aged twenty-nine years, who had been jaundiced since birth, and with the exception of transient constipation had never felt sick. The authors attributed the congenital form of icterus to a hereditary infirmity, a kind of degenerescence of the liver cell which leads to increased formation of bile (*diabète biliaire*). The father of this patient had an enlarged liver due to alcoholism. Vaques found an enlargement of the blood cells in this patient, which he attributes to the penetration of foreign substances into the body of the corpuscles. He could demonstrate an imbibition of the bile pigment into these corpuscles.

**Hypertrophic Cirrhosis of the Liver and Leukæmia.** Bigart<sup>2</sup> found a disturbance of the hæmatopoietic functions, an increase of the myelocytes from the normal, which is 0.5 per cent., to 20.6 per cent. in Hanot's liver cirrhosis. This he does not conceive to be one of the ordinary forms of infectious leucocytosis, but a peculiar variety of leukæmia. Further on he draws analogy between hypertrophic liver cirrhosis and leukæmia.

Among the most helpful clinical researches for the general practitioner are those which throw light upon the precursory stages of gastric disease that lead up to catarrhal jaundice, icterus, and cholelithiasis. Naturally this relation emphasizes the far-reaching value of prophylactic treatment. As cholelithiasis is recognized among the most frequent causes of cancer of the gall-bladder, it is conceivable how the cure of a chronic gastritis may prevent development of malignant disease of the gall-bladder. It is for this reason that the following researches of Simnitzki are cited with some detail.

**GASTRIC DIGESTION IN ICTERUS.** S. S. Simnitzki<sup>3</sup> concludes: 1. That in jaundice, as in all cases of retention of bile in the organism, the gastric function is affected, a hypersecretion being established. This overwork brings about a peculiar condition of the secretory gastric cell—its asthenia. 2. The gastric secretory activity is alike both in acute and in chronic jaundice—*e. g.*, when the latter appears in connection with hypertrophic cirrhosis of the liver—provided that no changes in the activity of the secretory gastric cells had occurred previous to the appearance of the jaundice. 3. In chronic jaundice—*e. g.*, when it appears in connection with hypertrophic cirrhosis of the liver—there are stages of transition in the activity of the secretory

<sup>1</sup> Soc. méd. des hôp., November 21, 1902.

<sup>2</sup> Comptes rendus de la société de biologie, No. 37.

<sup>3</sup> Russki Wratsch, 1903, Nos. 1 and 2.

gastric cell from hypersecretion to hyposecretion, the latter sometimes very pronounced. These phenomena are the results of the same condition of the secretory gastric cell, its asthenia appearing only in different degrees and periods. 4. The diminution of the acid secretion of the secretory gastric cells during certain stages of hypertrophic cirrhosis of the liver with jaundice, while the peptic secretion remains the same, would tend to prove that the peptic secretory activity of the stomach is of a stronger and more resisting character than its acid secretory activity.

Whenever jaundice is not complicated with distinct gastric catarrh a condition of high hyperacidity was noted in the stomach contents after a test breakfast. The hyperacidity was demonstrably due to hypersecretion, and experiments on dogs confirmed these clinical observations. In harmony with Pawlow's scholarly and important researches Simnitzki attempts to explain these alterations by postulating a diseased or asthenic state of the gastric secretory cell, due to poisoning with biliary products. Incidentally some interesting facts were noted. The well-known preference shown by icteric patients, human and animal, for carbohydrates and their aversion to meats or fats could be accounted for by the influence of the latter upon digestion. It was found, namely, that albuminous food retarded the passage of gastric contents into the intestine and produced certain irritative phenomena, like vomiting, diarrhoea, etc., while carbohydrates did not alter the secretions and the motor activity. The diet usually prescribed in icterus (milk and carbohydrates) was very well tolerated, thus showing a complete harmony of empirical and experimental data. These results, obtained from a study of acute jaundice, apply with equal force to chronic icteric conditions as seen in hypertrophic hepatic cirrhosis, etc. A gradual transition from gastric hypersecretion to hyposecretion has been noted in protracted jaundice, and is due to the same cellular asthenia in its carrying grades and stages. When gastric acidity is thus seen to fall the peptic power of the stomach remains unabated, justifying the conclusion that the pepsin-producing activity has a greater stability than the secretion of hydrochloric acid.

These results of Simnitzki are in agreement with my own,<sup>1</sup> published in 1898, in which I found, in sixteen cases of catarrhal jaundice, the following state of the gastric secretion.<sup>2</sup> In twenty-two cases of icterus free and combined HCl were absent in twelve, free HCl absent but combined present in four, free and combined HCl present in six. I

<sup>1</sup> Dietetic and Medicinal Treatment of Icterus and Cholangitis. Bulletin of University of Maryland Hospital, 1898, p. 31.

<sup>2</sup> Hemmeter. Diseases of the Stomach, 3d edition, p. 391. (By the time the third edition was published the studies had extended to twenty-two cases.)



have repeatedly emphasized that it would be important to know whether those cases in which the free HCl was absent during the icterus had chronic gastritis before the jaundice. I was able to trace up the later history of six of eight cases whose gastric secretion contained no free HCl during the jaundice. Two months after recovery from the attack they had a normal gastric secretion, and there were no evidences of gastritis.

The important clinical deduction to be made from these researches is mainly one of prophylaxis, it being established that chronic gastritis can cause catarrhal duodenitis, and this in turn may stenose the common gall-duct and also the pancreatic duct. We must look upon the catarrhal state of the stomach as the source of all this evil, and in my opinion many operations for gallstones will be prevented by a timely cure of the chronic gastritis which may precede it by years.

**Clinical Value of the Urinary Signs of Hepatic Insufficiency.** L. Ingelrans and M. Dehon<sup>1</sup> report the results of an investigation into the value of certain urinary signs considered to be indicators of hepatic insufficiency. They investigated the so-called alimentary glycosuria, the total nitrogen of the urine—hypoazoturia, hyperammonuria, urobilinuria, and indicanuria. Sixteen persons having various hepatic lesions and three healthy persons formed the basis of the investigation. The principal conclusions reached are: 1. Alimentary glycosuria is frequently absent in diseases of the liver, even when the parenchyma of the organ is markedly altered. Its absence, then, simply proves that the glycogenic function of the liver is still retained. 2. Hypoazoturia is nearly constant when the liver is anatomically altered. 3. While it is possible that hypoazoturia and fluctuations in the azoturic ratio may not be sufficient grounds on which to affirm hepatic insufficiency, these two signs are of great value in calling the attention of the clinician to the state of the liver. 4. Indicanuria is a sign of secondary importance. 5. Urobilinuria appears to be a sign of cholæmia and not of hepatic insufficiency. 6. The signs of hepatic insufficiency are not constantly united in any one patient. The functions of the liver are readily disassociated, and one may be at fault while the others remain in good condition.

**Concerning the Antitoxic Action of the Liver.** P. Teissier,<sup>2</sup> in studying the effects of the liver glycogen in watery solution on various poisons, found that it very much diminished the toxicity of nicotine, had no influence on strychnine, and actually increased the toxic influence of diphtheria poison.

<sup>1</sup> Archiv. de méd. expér. et d'anat. path., March, 1903.

<sup>2</sup> Recherches sur l'action antitoxique in vitro du glycogène hépatique. Soc. de biol. séance du 29 déc., 1900. La semaine méd., 21e année, No. 1.



When such results are submitted to critical judgment we find that exact conclusions concerning hepatic insufficiency are difficult to form.

**The Liver of the Dyspeptic; Dyspeptic Cirrhosis.** Contrary to the opinion of Emile Boix,<sup>1</sup> in which he asserted that cirrhosis could be produced by autointoxication of gastrointestinal origin, E. Nalin<sup>2</sup> denies that dyspepsia can produce the anatomical changes underlying the clinical picture of hepatic cirrhosis. According to Nalin, a morbid infirmity or predisposition of the lymphatic organs of the liver is necessary for the development of cirrhosis. He does not deny, however, that dyspepsia may cause inflammatory changes in the liver of a mild nature.

**Experimental Amyloid Degeneration of the Liver.** Stefanowitsch<sup>3</sup> has produced amyloid degeneration of the internal organs in rabbits and chickens by injecting a three days' bouillon culture of staphylococcus aureus twice weekly. A number of the animals were killed at the end of one month, and particles of the amyloid liver, spleen, and kidneys sewed into the subcutaneous areolar tissue. It was found that the amyloid substance was surrounded by a granulation tissue and converted into hyaline granules which eventually gave no amyloid reaction. Stefanowitsch assumes, therefore, that amyloid degeneration may undergo a spontaneous healing in the human being if the causes that have led up to it are removed.

**Latent Fatty Degeneration of the Liver** is more frequent than generally supposed, and much more common, without doubt, than all varieties of cirrhosis which develop as a result of the effect of alcohol upon the liver. This condition deserves an important place in pathology because it occurs quite frequently in young people as a concealed infirmity which inevitably aggravates the prognosis of otherwise benign diseases with which they may become infected. General practitioners have no doubt been frequently puzzled at the terrible struggle for life which young obese patients have to undergo in typhoid fever and pneumonia. The heart and the vessels are generally sound, and yet the gravity of what seems otherwise a very curable infection is inexplicable unless we assume the existence of a latent fatty degeneration of the liver. The prognosis of such infectious diseases, as well as of traumatic injuries and surgical intervention in young obese patients, must be very reserved. Of course the conception of latent fatty degeneration explains the variable course of any intercurrent diseases. As regards the recognition of such a condition, it is, of course, very difficult, and can only

<sup>1</sup> The Liver of Dyspeptics. Paris, 1897.

<sup>2</sup> Osservazioni ed esperienze sulla cirrosi del dispeptici. Klin. Beobachtungen über die Cirrhose der Dyspeptiker. Il Morgagni, Anno 44, parte i. H. 2.

<sup>3</sup> Russki Wratsch, 1903, No. 6.

be arrived at by exclusion. (Gilbert and Lereboullet<sup>1</sup> call attention to this condition and promise a more detailed description of it in a future communication. As a rule, the condition is found in young obese patients who are not in an age which alcoholic cirrhosis usually develops. In fact, they seem perfectly sound and apparently not suffering under their alcoholism until an intercurrent disease attacks them, which produces such gravity that it is out of all proportion to the degree of the infection.

**Healed Cirrhosis of the Liver ; Histological Examination of the Liver After Death by Erysipelas.** At the autopsy of a man who had suffered from ascites, œdema of the ankles, and icterus (the abdomen had been punctured twice) Apert<sup>2</sup> found a thickening of the capsule of the liver, a cirrhosis, presenting microscopically considerable vascularization of the perilobular connective-tissue bands. There was an angiomatous dilatation of the capillaries in many lobules. *The circulation between the vena cava and the portal vein had been completely restored.* Galliard<sup>3</sup> reports the cure of an advanced cirrhosis of the liver in a female patient after all other treatment had failed. The cure was effected by giving 150 gm. of pig's liver daily.

**Is the Gall-bladder a Useless and Dangerous Organ?** This is the title of a paper by Dr. Woods Hutchinson.<sup>4</sup> This article, together with one by Dr. Roswell Park, which appeared in *American Medicine* a few months previously (entitled "Why Not Treat the Gall-bladder as we do the Appendix?"), forced upon us the consideration of the question whether the gall-bladder is really a useless and dangerous organ. Hutchinson thinks he is "comparatively safe in saying that the principal secretions of the gall-bladder are mucus and gallstones." This statement is made in apparent disregard of the fact that the epithelial cells of the gall-bladder secrete cholesterol, the normal quantity of which can under pathological conditions be trebled (from 0.12 gm. to 0.334 gm. in the dog—C. A. Herter), and that calcium salts are secreted from the epithelial cells of the gall-bladder, and that the same irritants which increase the cholesterol can also increase the calcium salts, which is significant, for if the calcium is increased beyond a certain point it is liable to combine with bilirubin and produce a compound known as bilirubin-calcium, which forms the nucleus of a great many stones. It must, however, be emphasized that the normal gall-bladder cannot form stones. It is only the diseased gall-bladder which can produce them, or at least aid in their formation, and one of

<sup>1</sup> La stéatose hépatique latente alcoolique. *Gaz. hebdomadaire de médecine et de chirurgie*, 1902, S. 50.

<sup>2</sup> *Soc. méd. des hôp.*, January 16, 1903.

<sup>3</sup> *Ibid.*, January 23.

<sup>4</sup> *New York Medical Record*, May 16, 1903.

the essential factors in their etiology is the presence of bacteria. As long ago as 1876 Chareot and Gombault<sup>1</sup> found spores and bacteria in the bile after ligating the common duct in dogs. Netter,<sup>2</sup> after aseptic ligation of the common duct in rabbits, obtained cultures of bacteria from the bile. The staphylococci and streptococci were found by Netter and Martha (1886), Brieger, v. Leyden (1886), and others, in the human biliary passages, together with the bacterium coli communi. Naunyn, in his classical treatise on cholelithiasis, published in 1892, states that he had in the previous year gained the bacterium coli from the gall-bladder by a puncture during life in five cases of cholelithiasis. These historical statements are made because they seem to have been forgotten in the discussion during the symposium on gallstones at the Congress of American Physicians and Surgeons in Washington, May, 1903, and the original observations of bacterial findings in bile and gallstones erroneously attributed to others.

That the bile is chiefly excretory there can be no doubt, but this does not preclude the possibility that it may also in some way aid in the digestive process. The probable uses and functions of bile are given in my work, *Diseases of the Intestines*, vol. i. p. 48; more fully in the *American Text-book on Physiology*, and in Hammarsten's *Lehrbuch der physiologischen Chemie*. But we are by no means compelled to formulate opinions concerning everything we know or do not know regarding the probable digestive function of the bile. Much must be left for future physiological investigation. It is premature to deny every digestive action of the bile at the present time. Haller<sup>3</sup> states that in the entire animal kingdom the bile-duct enters the intestinal canal near its beginning, and he suggests that this demonstrates that the secretion must be of some digestive importance. If it were not nature could have arranged the gall-duets to discharge into the colon or rectum. The question, however, of the probable digestive function of bile has no direct bearing upon the question of the function of the gall-bladder. The gall-bladder has been considered a dangerous organ (1) because it is asserted that the gallstones are formed in it, and (2) because of its liability to disease. The first assertion, that gallstones are formed exclusively in the gall-bladder, disregards the fact that gallstones are found during operation and at autopsies in the intrahepatic bile-duets. Beck's skiagraphs proved the frequency of intrahepatic calculi, and these determined the frequency of recurrences of cholelithiasis even where the gall-bladder had been cleared of gallstones by operation. Cases are on record where the common gall-duct, the cystic duct, and the gall-

<sup>1</sup> Archiv. de phys. norm. et path., 1876, p. 453.

<sup>2</sup> Progrès médical, 1886, p. 992.

<sup>3</sup> Elementa Physiologic.



bladder were entirely free of concretions, and only intrahepatic gall-stones were found.<sup>1</sup> Of course, such intrahepatic calculi may be due to a precursory bile stagnation and dilatation of the larger vessels above mentioned, but it shows the possibility of formation of such stones outside of the gall-bladder. *The great liability of the gall-bladder to disease is no proof of its uselessness, for if there were no gall-bladder all the infections which eventuate in cholelithiasis would travel directly into the hepatic substance and there give rise to much more serious inflammation. The gall-bladder interposes itself between the bacterial hordes of the intestine and the liver.* Moreover, let us assume what would happen in a simple catarrhal stenosis of the papilla of Vater. As long as the bile can flow out, although in never so reduced a quantity, it will not enter into the pancreatic duct, for the pressure in the duct of Wirsung is about equal or a little greater than that in the common gall-duct. The liver has very little or no elasticity, the intrahepatic vessels a small degree of elasticity. If the liver is considerably distended we get what is called a stagnation cirrhosis, an inflammation of the liver due to the backing up of bile—*Die "Gallenstaunungscirrhose"* of the Germans. This would probably happen every time a human being has an acute or chronic gastritis that extends to the duodenum, and what prevents it, perhaps numberless times in the life of every individual, is the gall-bladder, for when the papilla of Vater or the diverticula of Vater is stenosed by catarrhal swelling it offers itself up as a transient reservoir for the surplus of bile capable of being largely distended by virtue of its elasticity, and the more distended it becomes the greater is the intrahepatic bile pressure, which eventually may become so great as to expel an obturating plug of mucus or small concretion. Moreover, we know from the researches of Opie and others that bile once forced into the pancreatic ducts may give rise to pancreatitis. Here, again, the gall-bladder may offer itself up as a temporary safety-reservoir, saving both the liver and the pancreas from dangerous bile pressure. Possibly many times in our lives we have been saved from pancreatitis and cirrhosis by the gall-bladder, and we did not even know that we were threatened by such complications.

Because the gall-bladder can be removed surgically in patients having suffered from cholelithiasis by no means proves that it is a useless organ in the normal being. To the patient in whom gall-bladder resection becomes necessary this organ has more than likely done its duty many times over, and has become diseased in consequence thereof, and if eventually it is diseased in this manner it is of course better to

<sup>1</sup> O. Leichtenstern. Die intrahepatischer Cholelithiasis. Penzoldt's u. Stintzing's Handbuch d. spec. Therapie inn. Krankheiten, Band iv., part ii. p. 60.



remove it, just as it is better to remove a suppurating or dead tooth. Moreover, the remote history of such patients in which gall-bladder extirpation has been performed has not yet been carefully studied, nor their future experiences recorded. That they can live without a gall-bladder for a year or more under careful dieting and hygienic living does not prove that the gall-bladder has been a useless organ. It must be first seen whether at the autopsy of such individuals the liver has not after all become the fundamental cause of their death.

Hutchinson<sup>1</sup> thinks that we are coming to regard the gall-bladder as a possible source of intestinal or gastric disturbance in a very large percentage of our cases, particularly the motor disturbances of the stomach. He even goes so far as to suggest that in 70 per cent. of all forms of ulceration which will be found in three or four inches of the pylorus are in this region because infection could be readily diffused there from a leaking gall-bladder. Exactly the reverse of this is what I am disposed to conceive. Gastric disturbances are in the majority of cases not the result but the cause of cholecystitis, by virtue of an extension of the catarrhal gastritis into the duodenum. Except in the case of duodenitis due to cutaneous burns, all other forms are due to extension of acute or chronic gastritis or other anatomical alterations of the stomach. It is from this standpoint that we can recognize the practical value of prophylaxis. If all gastric catarrhs could be recognized and cured we should have very little catarrhal jaundice and hear very little of gallstones, for it is the duodenitis that predisposes to the infection of the bile-ducts. There may, of course, be infections of the duodenum from the lower regions of the intestines, as occurs in typhoid fever, the various dysenteries, and possibly as a consequence of appendicitis; but by far the great majority of the infections come from the stomach, as a careful anamnesis and record of chemical and microscopic analysis of the gastric contents have convinced me in the great majority of my cases of cholelithiasis.

Of course it must be admitted that stenosis of the pylorus can be due to adhesions set up by a diseased gall-bladder, and numerous examples of such cases have been operated by surgeons after my diagnosis pointing to this etiology was expressed; but even in such cases the original cause of the disease may have begun in the stomach. As to the etiology of gastric ulcers having anything to do with an infection from the gall-bladder, I need only refer to the standard text-books on diseases of the stomach to show the current opinion of clinicians and pathologists concerning the pathogenesis of peptic ulcer. The essential factor for the production of a peptic ulcer is a hyperactive gastric juice.

<sup>1</sup> Medical Record, May 16, 1903, p. 772.

They may occur in the lower œsophagus, where bile cannot enter except it is vomited. Adhesions of the pylorus with the gall-bladder and consequent stenosis of the pylorus, with possible gastric hemorrhages and perhaps also the vomiting of bile, may have given rise to this confusion that peptic ulcers could be due to gastric infection with bile. In cases of gastropexia with almost constant presence of bile in the stomach I have never observed the development of a gastric ulcer.

**Relation of Cholelithiasis to Acute Pancreatitis.** Following the work of Eugene L. Opie, demonstrating that entrance of bile into the pancreatic duct could set up pancreatitis, J. Wiener, Jr.,<sup>1</sup> reports a case of acute pancreatitis due to cholelithiasis, and gives notes of thirty-two others. In all such cases an early exploratory laparotomy is the only correct course to pursue. The subject will be more minutely considered in the article dealing with pancreatic diseases.

**The Medical Diagnosis of Affections of the Gall-bladder.** Dr. John H. Musser<sup>2</sup> separates the primary and secondary affections of the organ. The primary are the catarrhal and infectious inflammations, neoplasms, and parasitic invasions by the echinococcus and round worms. The secondary affections are cholelithiasis, obstruction of the gall-ducts, and the suppurative inflammation of the gall-bladder and its surrounding vessels. Early recognition of the primary states would prevent the development of the secondary conditions. Of this there can be no doubt from what I have said concerning their pathogenesis in the preceding. Musser even went so far as to predict that in fifty years there would be little seen of these secondary conditions. As the management of the primary conditions is almost entirely clinical and not surgical, this emphasizes the value of the treatment of the derangements of the stomach and duodenum which generally precede cholelithiasis. Suppurative cholangitis, he said, was based upon a preceding development of gallstones or parasitic invasion. He has found leucocytosis in all the cases of suppurative cholangitis he has seen, and he calls attention to the occurrence of tenderness about the twelfth dorsal vertebra as an aid to the diagnosis of suppurative diseases of the biliary passages. The differential diagnosis must distinguish between abscess of the liver, congestion and engorgement, pyelophlebitis, subdiaphragmatic or subphrenic abscess, diaphragmatic pleurisy, pneumonia, disease of the pancreas, perforation and obstruction of the intestine. In connection with the tenderness about the twelfth dorsal vertebra, to which Musser refers, I must call attention to an article by I. Boas,<sup>3</sup> in which he extends

<sup>1</sup> New York Medical Journal, May 16, 1903.

<sup>2</sup> Symposium of the Congress of American Physicians and Surgeons, Washington, May 13, 1903.

<sup>3</sup> Beiträge zur Kenntniss der Cholelithiasis. Münchener med. Wochen., No. 15, 1903.

the dorsal area of sensitiveness to pressure over the entire posterior surface of the liver, from the two lower thoracic vertebræ to the first lumbar vertebra, and from the posterior axillary line to within 2 cm. to the right of the spinal column. This sensitiveness to pressure is of diagnostic importance for swelling of the liver as well as acute and latent cholelithiasis. Boas attributes his sign to perihepatic processes. In order to determine the various degrees of dorsal pressure sensitiveness we may make use of the faradic current, placing both electrodes near each other at congruent places. The dorsal sensitiveness may exceed in duration the acute attack of gallstone colic by several weeks or months, and during all this time the patient must be kept under careful surveillance. The emphasis which Boas lays upon the conviction that the pain is due to perihepatic (peritonitic) processes brings to mind the valuable paper of R. Tripier and J. Paviot.<sup>1</sup> The old view has been that the pain of hepatic colic is due to the passage of a gallstone, but the clinical and post-mortem observations of Tripier and Paviot led them to the conclusion that affections of the abdominal organs only give rise to painful crises when their enveloping peritoneum is acutely or subacutely inflamed, and that the pain varies inversely with the amount of the exudate. These authors, in a previous publication, have shown this to be true of the appendicular crises, and now assert that it holds good for hepatic colic, viz., that this pain is also due, in their opinion, to inflammation of the peritoneum in the region of the liver and gall-bladder, and the occasional clinical similarity of appendicitis and other inflammations by gall-bladder affections is thus easily explained by a propagation toward the appendix and other organs of a peritonitis having its origin in the environment of the gall-bladder.

These papers of Boas and Tripier and Paviot were not referred to in the paper by Dr. John H. Musser.

**Etiology and Pathology of Gallstones.** C. A. Herter's<sup>2</sup> report presents little that is new which cannot be found in the recent works on pathology and pathological physiology or clinical pathology.<sup>3</sup> Herter has conducted experiments to see if it were possible to increase the cholesterin by the production of an artificial cholecystitis. It was found that by the injection of chemical irritants (mercuric chloride and phenol) the cholesterin could be increased from 0.12 to 0.298 or

<sup>1</sup> Concerning Peritonitic Pathogenesis of Hepatic Colic and Painful Epigastric Crises. *La semaine médicale*, January 28, 1902.

<sup>2</sup> Symposium of the Congress of American Physicians and Surgeons, Washington, May 13, 1903.

<sup>3</sup> Hammarsten, *Physiologisches Chemie*; Ribbert, *Lehrbuch der spec. Pathologie*; Krehl, *Patholog. Physiologie*; Naunyn, *Die Cholelithiasis*.



0.334). Herter is inclined to think that the bile may become infectious in infectious diseases like lobar pneumonia, and that this infectious bile of itself may set up infection of the gall-bladder. It is probable that any condition of cholecystitis bringing about a pathological alteration of the epithelium of the gall-bladder was liable to be attended by an increase in the amount of calcium in the bile, which, if it exceeded a certain quantity, would precipitate bilirubin calcium by combining with the bilirubin. The bacterial nidus of the gallstones, the original discovery of which he appears to attribute to Welch in 1890, was in reality first observed by Charcot and Gombault,<sup>1</sup> and later on by Netre and Martha, Brieger, v. Leyden, and Naunyn. An intensely interesting history of this bacteriological work on gallstones will be found in Naunyn's classical treatise on *Cholelithiasis*, translated by Archibald E. Garrod for the New Sydenham Society, pp. 46-52. In the above paper C. A. Herter emphasized that the two essential conditions for the formation of gallstones are the entrance of pathogenic micro-organisms and the stagnation of bile. With regard to the constitutional origin of gallstones, he had made some experiments on dogs, feeding them almost entirely with fat, and at the end of three months minute masses of bilirubin calcium were found in the gall-bladder, and in one instance there was a distinct concretion. He had never before met with such a concretion in over one hundred gall-bladders examined by him in other dogs. It is important to note out of deduction from this valuable report that it was possible to largely increase the quantity of cholesterol, by means of chemical irritants, without the presence of an infection, and, secondly, that constitutional conditions may bring about such chemical changes in the bile, that it constitutes an irritant to the bile passage, may play an important part in the pathogenesis of cholelithiasis.

**Diseases of the Gall-bladder and Bile-ducts with Special Reference to Diseases of the Stomach and Intestines.** This subject was considered by Prof. C. A. Ewald,<sup>2</sup> of Berlin. Under this heading one would naturally expect to find a presentation of those abnormal conditions of the stomach and intestine which could be productive of disease of the gall-bladder by causing disease of the mucous membrane of the duodenum, for considered from the standpoint of topography the pathogenesis of cholelithiasis could be considered from two aspects: (1) the catarrhal extensions and bacterial invasions from the duodenum causing disease of the epithelium of the biliary apparatus; (2) metabolic or

<sup>1</sup> Archiv d. Physiologie normal und Pathologie, 1876, p. 543.

<sup>2</sup> Symposium of the Congress of American Physicians and Surgeons, Washington, May 13, 1903.



chemical changes in the excretion of the bile caused by infectious diseases or altered metabolism, as pointed out by C. A. Herter,<sup>1</sup> and changing the quality of the bile chemically so as to constitute an irritant. Ewald has found the internal treatment of cholelithiasis very unsatisfactory, and he looked upon the surgical treatment of this disease as being very much in the same position as that of appendicitis. Not all cases of appendicitis were necessarily to be treated surgically, and the same is true of cholelithiasis, in Ewald's opinion. He also emphasized that even by operation one could not be sure of a recurrence, which is quite intelligible when one reflects that with removal of the gallstones we do not remove the disease, but the result of the disease. If the disease itself is remediable—for instance, infection of the gall-bladder—it is possible to cure this by surgical means; but if it is due to some metabolic and chemical change in the secretion of the bile, I do not see how a surgical operation could cure it, although even in such cases the surgical removal is an absolute necessity in order to prevent further complications (pancreatic disease). But after such operations the patient should be recommended to the care of a competent clinician to make a study of his metabolism, and by examination of the stools and stomach contents keep informed concerning the state of the gastrointestinal canal.

**The Medical Treatment of Cholelithiasis.** From what we have learned in the preceding we may conclude that the radical treatment of cholelithiasis is not identical with the removal of the gallstones, but with the healing of the inflammatory process or infection that has either travelled up from the duodenum or the metabolic abnormality which has changed the composition of the bile. This is proven by the fact that gallstones may re-form after their surgical removal, and, again, by the fact that spontaneous cures may occur where the stones remain in the gall-bladder and are found there after death from some other disease, the patient never having complained of the symptoms of cholelithiasis. Riedel<sup>2</sup> states that in Germany 2,000,000 human beings carry gallstones in their gall-bladder, but of these only 100,000 have cholelithiasis. Evidently there must be self-healing mechanisms in the hepatic and biliary apparatus whereby the gall-bladder, far from being always a menace to life and a useless organ, may actually be a preserver of life by retaining and holding gallstones, which, if they moved out of it, would become dangerous. Ludwig v. Aldor<sup>3</sup> gives the internal treatment of gallstone disease, laying especial stress upon the Carlsbad

<sup>1</sup> Loc. cit.

<sup>2</sup> Penzoldt u. Stintzing's Handbuch d. Therapie, Band iv.

<sup>3</sup> Die innere Behandlung der Gallensteinkrankheit. Archiv f. Verdauungs-krankheiten, Band iii. p. 622.

cure, which is, however, in this case, employed in an entirely different manner from that usually recommended. The stereotyped Carlsbad cure includes extensive physical exercise, long walks, together with the drinking of the water. It is this physical exertion which may actually induce an attack of hepatic colic by starting the exit of a stone from the gall-bladder into one of the ducts, and explains the impressions gained by Carlsbad patients that a Carlsbad cure is effected only at the expense of several attacks of hepatic colic. No doubt many of these patients who are ordered to take long walks on the seductive serpentine promenade of Carlsbad have circumscribed peritonitis, and their condition is only made worse by the exercise. Ludwig v. Aldor keeps his gall-stone patients in bed from 7 o'clock in the morning until 12 o'clock, and from 2 o'clock in the afternoon until 7 o'clock in the evening, applying hot external applications in the shape of comfortably fitting zinc abdomen warmers. Every two hours the patient drinks from 150 c.c. to 200 c.c. Sprudel Wasser of 55° C. The daily quantity consumed varies from 700 c.c. to 1½ litres. The patient is not directed to starve himself, but receives a mixed and quite liberal diet, excluding only the highly seasoned, spiced, and stimulating food. This simple rest treatment is kept up until all sensitiveness to pressure over the hepatic region has disappeared. The time required for this treatment was five weeks in the majority of cases. Ludwig v. Aldor does not claim that the Carlsbad waters have a stimulating effect on the secretion of bile, nor that they can dissolve gallstones, and, therefore, I may be permitted to suggest that we Americans do not need the Carlsbad water at all for this purpose, and could carry on the treatment as well with the Saratoga Carlsbad or the magnesia spring of Bedford, Pa.

F. Blum<sup>1</sup> speaks very highly of the sodium oleate which has been brought into commerce, under the name of "eunatrol," for stimulating the secretion of bile in cholelithiasis. He associated this remedy given in the form of chocolate-coated pills, in doses of 0.25 gm., with high enemata of olive oil.

We have hitherto only recognized two remedies as having influence in stimulating the bile, namely, the bile salts and the salicylate of sodium. A. Chauffard<sup>2</sup> lauds the salicylate and the benzoate of sodium as the best remedies for the internal treatment of cholelithiasis. He combines it with the internal use of Harlem oil, giving the salicylate of sodium in daily doses of 1 gm. or 2 gm. (15 gr. or 30 gr.) in conjunction with an equal amount of sodium benzoate. This medication is given ten to twenty days every month for many months, even years.

<sup>1</sup> Die ärztliche Praxis, 1902.

<sup>2</sup> Du traitement médical préventif des coliques hépatiques à répétition, Hôpital Cochin. La semaine méd., 21e année, No. 1.

Only by great persistence can the desired results be effected, and Chauffard considers the treatment so beneficial that most cases of cholelithiasis in his experience were healed without surgical intervention.

The great danger of the complications of cholelithiasis—pancreatitis, carcinoma of the gall-bladder, peritonitis, hepatitis, etc.—should make us especially skeptical with regard to such claims; and although the symptoms of cholelithiasis may be much improved by internal treatment, the life of the patient is safer with the gallstones removed surgically.

**Diagnosis of Liver Diseases.** A very able article on the "Differential Diagnosis of Certain Diseases of the Liver" is published by Charles G. Stockton.<sup>1</sup> This paper treats first of the differential diagnosis between *cirrhosis of the liver* and so-called *syphilitic cirrhosis of the liver*. In this paragraph Stockton defines his interpretation of the terms hypertrophic and atrophic cirrhosis. When the round-cell infiltration is specially intralobular it is said to be characteristic of hypertrophic cirrhosis, and clinically in such cases one would expect to find the liver increased in bulk and ascites present. On the other hand, when the connective tissue grows for the most part in the interlobular spaces around the radicles of the portal veins, and to some extent cuts off the supply of the portal blood to the liver, it is said to be characteristic of atrophic cirrhosis, and clinically one would expect to find in such cases the liver decreased in bulk and ascites present. Aside from the questionable method of arguing retrogressively—that is, from the post-mortem appearances to the clinical phenomena—these deductions present other debatable features, and, as Stockton emphasizes, the distinction between atrophic and hypertrophic cirrhosis is for the most part an academic question. Whether the changes described are intralobular or perilobular, an atrophy of the hepatic parenchyma is actually met with in both states, as Councilman has pointed out. From Stockton's description one would be strengthened in the belief that without the therapeutic test, namely, the administration of mercury and the iodides, the distinction between syphilitic cirrhosis and other forms of cirrhosis of the liver would be impossible. He admits that a transient benefit may come to non-syphilitic forms of cirrhosis of the liver from this treatment. If the assertions of the French writers are true, that the iodides and mercury will greatly improve any form of cirrhosis except that due to malignant tumor, then the therapeutic test is of little value as a diagnostic factor unless it is coupled with an undoubted specific history of the patient.

The second paragraph of this paper deals with the diagnosis between

<sup>1</sup> American Medicine, February 14, 1903.



*cholelithiasis* and *cancer of the liver*. In this section Stockton deals extensively with the publication of Hans Kehr, who emphasized that jaundice was absent in 80 per cent. of his cases of gallstones. *Courvoisier's law* is emphasized, viz., that when a stone is held at the juncture of the cystic and hepatic ducts the gall-bladder is even less likely to be enlarged, and when the concretion is retained at the outlet of the common gall-duct the enlargement of the gall-bladder is almost invariably absent. Courvoisier's law is practically as follows: The presence of jaundice with enlargement of the gall-bladder suggests cancer; on the other hand, with a history of gallstones and with the gall-bladder not palpable it suggests stone in the common duct. In cancer there is often very little evidence of inflammatory reaction, which state is so commonly observed in cholelithiasis. We must not expect to make a positive diagnosis in all cases, even when one of the affections is unaccompanied by the other; but if we remember what has been said about the diagnosis of gallstones and recall that in cancer we generally find the liver large, jaundice present, the gall-bladder increased in size and palpable, a marked secondary anæmia and cachexia present, fever and biliary colic absent, Stockton thinks that we should usually be able to distinguish between these two affections.

The third section deals of the differential diagnosis between *cholecystitis* with *angiocholitis* and *abscess of the liver*. Of course, cholecystitis accompanied with angiocholitis may closely resemble suppurative hepatitis, and a diagnosis which would limit all possible hepatic disorders down to these two would under certain conditions not exactly be a bad diagnosis. Nevertheless, Stockton gives us some valuable hints which make even this differential diagnosis possible. The anamnesis is important for hepatic abscess. Dysentery and typhoid fever have been known to give rise to it. A previous history of attacks of pain and other characteristic phenomena previously mentioned is suggestive of cholecystitis.

In angiocholitis jaundice is most invariably present. Jaundice is rarely present with abscess of the liver, and in the exceptional cases in which it does occur it is due to an accompanying angiocholitis or pressure upon one of the larger bile vessels. Stockton is enthusiastic on the efficacy of puncture for the diagnosis of abscess of the liver. He has seen no injury come even from repeated punctures of the liver. His chief factors in the diagnosis for hepatic abscess are the following: Enlargement of the upper rather than the lower border of the liver, inflammation of the pleural cavity, jaundice more frequently slight or absent, may possibly be severe; tenderness, possibly perihepatitis; fever of varying type, leucoeytosis, previous history as to causation, and, finally, the outcome of puncture.



In the fourth and last section of this interesting paper Stockton speaks of the differential diagnosis between the *sclerosis of the liver* following chronic biliary obstruction and the so-called *Hanot's sclerosis* of the liver. There can be no doubt that these are two distinctive forms pathologically, but whether or not they can be separated clinically is doubtful.

In the discussion of Hanot's cases by Charcot, the latter accounted for the hepatic changes by the angiocholitis that existed, and explained the increase in the size of the liver, and the fatal termination, by the retention of bile which resulted; this explanation of Charcot made things worse, in Stockton's opinion. He states: "Undoubtedly the confusion was worse confounded by Charcot's discussion."<sup>1</sup> The clinical distinction between *hypertrophic cirrhosis* of the liver and *Hanot's cirrhosis* of the liver is a diagnostic conundrum which Stockton bravely attempts to solve. In the former we have to deal with a condition which results from obstruction to the bile-ducts from any cause whatsoever—from obstructing gallstones, adhesions, pressure from tumors, or long-continued inflammatory processes involving the biliary channels; and no matter from what cause we have a resulting stasis of bile, moderate enlargement of the liver, jaundice, with the usual symptomatology of cholæmia. Some cases are complicated by connective-tissue changes, such as occur in simple atrophic cirrhosis, and in such instances ascites appears. On the other hand, ascites may be absent, while the jaundice remains intense. The features that are characteristic are continued jaundice, usually marked in character, moderate enlargement of the liver, with little or no change of the spleen.

Stockton promises us a future publication on *Hanot's cirrhosis*, but for the present recalls these diagnostic facts: A young person is suddenly attacked with abdominal pain, who has a very large, sharp-edged, smooth liver, having at the same time a very large spleen and accompanying jaundice, but no ascites; that he afterward improves, but the liver and spleen continue increasing in size, the jaundice never quite disappearing, but increasing from time to time, usually synchronously with elevation of temperature. Observe that this is a very chronic condition; that it is free from a history of alcoholism or other known cause of disease, and that though it may persist for several years the fatal outcome in icterus gravis is assured if we are to be guided by the history of recorded cases.

Another very recent publication on the "Diagnosis and Treatment of Gallstone Disease" is by D. D. Stewart,<sup>2</sup> of Philadelphia. Stewart

<sup>1</sup> American Medicine, February 15, 1903, p. 255.

<sup>2</sup> American Journal of the Medical Sciences, May, 1903.

has brought together a group of highly interesting cases of *catarrhal cholecystitis* with and without obstruction, of *dropsy of the gall-bladder* or *pericholecystitis* with adhesions, of *chronic obstructions of the common gall-duct by stones*, with what he calls the "usual" accompanying jaundice and shortened gall-bladder. From what has been pointed out in the previous papers, however, jaundice is not so "usual" in obstruction of the common gall-duct. Stewart's report is mainly one of casuistic nature, and must be read in the original to be appreciated. Regarding surgical interference in catarrhal cholangitis without presumed obstruction of the duct, he advises one or two seasons at Carlsbad if there is no family history of cancer. If the cholecystitis is recent and of mild type, and there is no persistent recurrence, he regards surgical intervention as yet unnecessary. With evidence of cholecystitis he regards the case as a surgical one immediately. He seems to be very fond of Carlsbad water, or the Carlsbad salt in powder or crystal form, especially for douching the stomach in gastric atony accompanying cholecystitis. He has discontinued the use of olive oil in obstructions of the common bile-duct by stones. The last paragraph of the paper is devoted to preparatory treatment before operation in obstruction of the common bile-duct by stone.

## DISEASES OF THE PANCREAS.

**The Anatomy and Physiology of the Pancreas.** The most recent and at the same time the most valuable contribution to this subject is a monograph by Dr. Eugene L. Opie.<sup>1</sup> I will pass over the description of the embryology and development of the pancreas as not of absorbing interest to the clinician. In his description of the two ducts, the larger one the duct of *Wirsung*, which enters the intestine in company with the common bile-duct, and the smaller or accessory duct, that of *Santorini*, which terminates in the papilla situated nearer the stomach than that of the larger duct, he emphasizes that the duodenal orifice of the accessory duct is very minute and joins the duct of *Wirsung*, into which, doubtless, it pours its contents in the great majority of individuals. Opie has dissected the ducts after injection in one hundred subjects. The two ducts were present in every instance, but one or the other was occasionally so small that it was found with difficulty. In ten of the one hundred instances the two ducts failed to anastomose within the gland, and in four additional subjects the two ducts were united by such a minute branch that they might be regarded as inde-

<sup>1</sup> The Anatomy of the Pancreas. American Medicine, June 20, 1903, p. 996; also journal articles by same author.

pendent of one another. In twenty instances the duodenal end of the duct of Santorini was not patent. Thus these figures demonstrate that in at least two-thirds of all individuals the duct of Santorini cannot act as an accessory outlet when the duct of Wirsung is occluded. In a considerable number of specimens the orifice of the duct of Santorini, though patent, was so minute that its functional significance was slight, and in eleven of the one hundred specimens the duct of Santorini, on the contrary, was equal in size or larger than the duct of Wirsung, so that during life it was doubtless the outlet for the larger part of the pancreatic juice. The two ducts unite to form the short common channel, the diverticulum of Vater, which is subject to almost as much variation as the pancreatic ducts themselves. In eleven instances of the one hundred subjects examined by Opie no diverticulum was present, and the two ducts entered the duodenum separately at the summit of the bile papilla. The duodenal orifice of the diverticulum of Vater had an average diameter of 2.5 mm., and the length of the diverticulum varied from 1 mm. to 11 mm., and only in thirty of the one hundred specimens did the length equal or exceed 5 mm. These dimensions are significant, because they show that a calculus which has become impacted within the orifice will completely fill the diverticulum and occlude both ducts.

Physiologists and pathologists are now more and more appreciating the two functionally diverse elements of the pancreas. First, cells which supply the intestine with important digestive ferments—those which are concerned in the manufacture of pancreatic juice—and, secondly, cells having no communication with the ducts of the glands, but in intimate relation with the bloodvessels, and producing an internal secretion concerned in carbohydrate metabolism. Cases have from time to time been reported in which it was claimed the entire pancreas had been destroyed by disease, and yet the carbohydrate metabolism did not appear disturbed. We can understand how the stomach and intestines may step in and take up the digestive functions of the pancreas vicariously, but this is not intelligible as far as the internal secretion is concerned. In such cases where the pancreas is apparently destroyed the maintenance of normal carbohydrate metabolism might be explained by the discovery of Helly, who found lobules of pancreatic parenchyma situated within the papilla of the duct of Santorini, and also immediately below the duodenal mucosa. Occasionally these misplaced portions of pancreatic tissue were provided with an independent duct, and constituted a true accessory pancreas.

In 1800 autopsies performed at the Johns Hopkins Hospital small masses of aberrant pancreatic tissue were found by Opie imbedded in the wall of the stomach or of the intestine in ten cases at a variable



distance from the pancreas. In two instances two accessory glands occurred in the same individual. These accessory and aberrant pancreatic glands may in exceptional cases explain the maintenance of normal carbohydrate metabolism in those exceptional cases where the pancreas was reported apparently entirely destroyed.

Proceeding to a consideration of the histology of the pancreas, Opie graphically describes the ferment-secreting cells, which are large and contain zymogen granules, presenting characteristic variations during different stages of secretion, and forming the secreting acini. Scattered among the secreting acini, and several times the size of a single acinus, are the round, oval bodies composed of polygonal cells grouped together to form short, tortuous columns, which unite with one another in such a way that space is left for a network of wide capillary bloodvessels. These interacinar islands are surrounded by capillary vessels which, when injected, appear tortuous, dilated, and resembling the glomeruli of the kidneys. These islands of Langerhans consist of columns of cells in intimate relation with a rich vascular supply, and having no communication with the pancreatic ducts. They are ductless glands resembling the adrenal and parathyroid bodies. They are not concerned in the elaboration of the pancreatic ferment, and abundant evidence has shown that the islands of Langerhans exert an influence upon the carbohydrate metabolism through an internal secretion. Opie describes the pancreas of a child who died of diabetes. The disease in this case was hereditary, and affected six members of the same family. The number of the islands of Langerhans was only a third of that usually and normally present. It suggests the possibility that diabetes will occasionally be the result of a congenital anatomical defect in the pancreas.

**Chronic Indurative Pancreatitis.** S. M. Melkich<sup>1</sup> reports two highly instructive cases of chronic pancreatitis. The true nature of the malady, however, was ascertained at the laparotomy. In a female, aged thirty-eight years, the principal symptoms were those of bile retention. In another, a woman aged twenty-two years, among many other symptoms the most poignant were violent attacks of colic with considerable elevation of temperature. This writer, in agreement with a former publication by myself,<sup>2</sup> and a very instructive paper by Reginald H. Fitz, to be reported in the following, asserts that the diagnosis of chronic pancreatitis presents immense difficulties and is, as a rule, not recognized before the autopsy. According to Melkich, this disease is either caused by alterations in the bloodvessels on the basis of alcoholism, syphilis, or arterial sclerosis, or, secondly, by bacterial and catarrhal processes, the latter frequently associated with formation of

<sup>1</sup> Praktischeski Wratsch, 1902, Nos. 38-41.

<sup>2</sup> International Clinics, 1902.



concretions in the excretory ducts. If we can establish the coexistence clinically of diabetes steatorrhœa and azotorrhœa in addition to a palpable enlargement of the head of the pancreas we should suspect an involvement of this organ. Unfortunately, these symptoms are rarely present simultaneously. He finds that the most constant clinical sign is tumor in the particular abdominal region—that is, a swelling of the head of the pancreas—which means that phenomena of pressure resulting therefrom—for instance, compression of the pylorus, icterus, passive congestion in the portal-vein system, ascites, and enlargement of the spleen, œdema of the lower extremities, and cœliac neuralgia—are provoked by pressure caused by increase in volume of the head of the pancreas. The differential diagnosis must consider the distinction from *catarrhal icterus*. A particularly stubborn icterus accompanying a palpable tumor in the region of the pancreas speaks for pancreatitis. An existing pancreatitis may simulate cholelithiasis. Here the following argument seems logical: chronic and slowly increasing icterus with simultaneous colics, enlarged gall-bladder with symptoms of protracted cholelithiasis, and an olive-green or yellowish discoloration of the skin speaks for pancreatitis, especially so when at the same time a tumor can be palpated in the pancreatic region. If carcinoma of the pancreas can be excluded and an operation produces improvement, these consequent effects of the laparotomy confirm the diagnosis of chronic indurative pancreatitis.

**Pancreatic Disease Simulating Cholelithiasis.** Since the work of Opie the physiological, embryological, and pathological relationship between the pancreas and liver has been more carefully studied. Worobjew<sup>1</sup> also emphasizes that the pancreas frequently participates in diseases of the liver, and, what is more important to know, it may closely simulate hepatic disease, particularly cholelithiasis. A complete clinical picture of gallstones may thus be present, due exclusively to chronic disease of the pancreas. Infrequently, also, both organs are affected, and we have reasons to surmise that the classical symptoms of biliary calculi are only in part due to the latter, the pancreatic component entering largely into the clinical picture. For the physician, and still more so for the surgeon, these facts carry the greatest weight. It has occurred that an operation was performed for "gallstones," and stones were removed from the gall-bladder, yet no improvement resulted, and at the autopsy calculi were discovered in the pancreas. Symptoms pointing to pancreatic involvement (chronic inflammations, calculi, etc.) are: (1) colicky pains in the left hypochondrium, unaccompanied by jaundice; (2) diabetic manifestations, chiefly rapid

<sup>1</sup> Chirurgia, January, 1903.

emaciation; (3) fatty evacuations; (4) salivation; (5) tumefaction and resistance in the region of the pancreas, and (6) the appearance of calculi in the stools following attacks of colicky pains, the calculi consisting of carbonates and phosphates of lime. As to treatment, narcotics are of value in pancreatic colic. Pilocarpine hypodermically and pancreatin internally deserve a trial, but in the event of failure recourse should be had to surgical measures.

In recent American literature two cases of *pancreatitis due to preceding cholelithiasis* are reported, one of acute pancreatitis with fat necrosis, by H. Monks and David B. Scannell, which terminated fatally after the operation. The pancreas and the left suprarenal body were disintegrated by fatty necrosis. The second case was one of chronic pancreatitis, and is reported by Harding.<sup>1</sup> It occurred in a woman, aged forty-nine years, who had previously had both breasts removed for cancer. The symptoms came on acutely, and consisted of severe pain in the epigastrium, lasting for four hours. Attacks of pain occurred every third day, associated with fulness in the stomach and frequent eructations of gas; jaundice, nausea, constipation, and neurasthenic symptoms were present. At the operation the pancreas was found enlarged and nodular, which led to the suspicion of cancer. A small piece of the pancreas was examined, but showed simply chronic pancreatitis and no cancer. Nothing was done except to open and drain the gall-bladder, and the patient recovered entirely.

Both of these recent cases from American literature emphasize the necessity of exploratory laparotomy as soon as such conditions are suspected.

**Diabetes and Diseases of the Pancreas and Liver.** Steinhaus<sup>2</sup> reports autopsy findings in twelve cases of cirrhosis of the liver. In eleven of these chronic interstitial inflammation of the pancreas was found. The character of the inflammation is not described with the same exactness that Opie gives to this subject. It is said to be a chronic interstitial inflammation of the pancreas similar in each case to the condition found in the liver of the same subject. The islands of Langerhans were found affected in only one case. The diminished tolerance for sugar frequently observed in cirrhosis of the liver is, therefore, probably due to the implication of the pancreas and not to the liver condition. It is not necessary to classify separately the glycosurias accompanying cirrhosis of the liver, arteriosclerosis, pancreatic disease, etc. Rather it is to be inferred from all recent investigations that every case of glycosuria is probably due to some disturbance in

<sup>1</sup> Washington Medical Annals, November, 1902, p. 357.

<sup>2</sup> Deutsche Archiv f. klin. Med., Band lxxiv., Heft 5 und 6.

the functions of the pancreas, and that this organ alone controls the carbohydrate metabolism of the organism.

**Symposium on Pancreas and Pancreatic Disease.** This symposium was led chiefly by E. L. Opie,<sup>1</sup> of Baltimore, on the anatomy and histology which we have already abstracted in the preceding. A second paper was the physiology and physiological chemistry, by Prof. R. H. Chittenden, of New Haven, who dwelt upon the two distinctive functions of the pancreas. He referred to the work of Bayliss and Starling, which we have already abstracted in the preceding. These observers separate from the duodenal mucosa a substance which they call "*secretin*," which converts the zymogens of pancreatic juice into active ferments. I wish to remark that these researches of Bayliss and Starling (see the report in the section on Physiology of the Intestines) have recently been confirmed by two French experimenters, Enriquez and Hallion,<sup>2</sup> who extend the physiological effects of secretin, and assert that it is not a specific stimulant for pancreatic secretion, but also stimulates the secretion of bile. They also assert that an acid as well as bicarbonate of soda, two antagonistic chemicals (acid and base), will produce an abundant flow of bile and pancreatic juice when brought upon the mucosa of the duodenum in dogs that have a duodenal fistula.

Chittenden does not furnish in his report satisfactory evidence that the cells of the islands of Langerhans have an internal secretion. The cells of the pancreas have more pentose than the other cells in the body. Chittenden called attention to the results of Herter and Wakeman concerning the adrenalin glycosuria, and the reducing action upon the pancreatic cells. The fact that many organs of the body might form reducing substances which might reach the pancreas in the blood stream threw a new light on the origin of diabetes. However, Herter and Wakeman<sup>3</sup> found that not only reducing substances but also oxidizing substances could cause glycosuria. Adrenalin when brought upon brain, liver, spleen, or kidney also produces increased excretion of sugar, and they could not positively prove whether or not this adrenalin had been absorbed into the general circulation and, after all, produced its effect by acting upon the pancreas, for to decide this it would have been necessary to extirpate the pancreas—a procedure which in itself inevitably causes glycosuria. So the present state of the physiology of the pancreas gives us no new and precise information on these important questions.

<sup>1</sup> Congress of American Physicians and Surgeons, Washington, May 12, 13, and 14, 1903.

<sup>2</sup> Recherches nouvelles sur la "*secretine*," Action sur le foie, Presse médicale, No. 7, 1903.

<sup>3</sup> American Journal of the Medical Sciences, January, 1903.



The experiments of Herter and Wakeman would receive a new interpretation if the statements of Poehl<sup>1</sup> could be confirmed concerning the derivation of the substance known as adrenalin. Poehl asserts that this substance does not by any means occur only in the adrenals, but in all other organs and tissues of the body. Poehl attributes the priority of having discovered adrenalin in 1892 to Kondratiew, who, it is claimed, made a strong solution of it from the spleen of animals. As long as the adrenalin is in the nucleus of the cells it is not only harmless, but of advantage to the organ. The poison<sup>1</sup> leaves the cell, according to Poehl, when the juices of the organism become acid, which can occur from certain forms of anæmia and diabetes. To avoid this exclusion of the poison from the cells the alkalinity of the juices must be restored.

#### **Symptomatology and Diagnosis of Diseases of the Pancreas.<sup>2</sup>**

The most valuable paper, from a clinical standpoint, that was contributed to the symposium,<sup>3</sup> was that on the symptomatology and diagnosis of disease of the pancreas, contributed by Prof. Reginald H. Fitz,<sup>4</sup> of Boston. Fitz began by a reference to the work of Friedreich in 1875.<sup>5</sup> According to Friedreich, no single symptom which may occur in diseases of the pancreas is pathognomonic, and the occurrence of several does not always result in a positive diagnosis. Fatty stools, melaturia, epigastric pain, with the characteristics of cœliac neuralgia and palpable tumor, lead among the symptoms most useful in diagnosis, and then follows a remarkable statement of Friedreich, which I have since his publication occasionally seen erroneously attributed to others, viz., "The presence of undigested striated muscle fibres in the feces is worthy of every consideration, and may prove of diagnostic value." Fitz agrees with other authorities that the symptoms and signs especially suggestive of pancreatic disease are dependent largely upon the resulting disturbances of (1) its functions and (2) upon the situation of the organ. The former include the various modifications in the composition of the urine and feces; the latter comprise the localized resistance, tenderness, and pain, and the evidence of obstruction of the gastrointestinal and biliary tracts. The demonstration of sugar in the urine, of visible fecal fat, or undigested muscle fibres in the feces often led to the assertion that pancreatic disease was present when one or more of these conditions had been determined. But when the results of clinical observation were compared with anatomical investigation it became evident that

<sup>1</sup> Die neuesten Untersuchungen über die chemischen Lebensprozesse in Verbindung mit der Frage der Bedeutung des Adrenalchlorids (Adrenalin). Russki Wratsch, 1903, No. 13.

<sup>2</sup> PROGRESSIVE MEDICINE, June, 1902, p. 111; December, 1902, pp. 60-64.

<sup>3</sup> Congress of American Physicians and Surgeons, Washington, May, 1903.

<sup>4</sup> American Medicine, June 6, 1903, p. 907.

<sup>5</sup> Ziemssen's Handbuch der speziellen Pathol. u. Therap.



diseases of the pancreas occurred much more frequently without the recognition of glycosuria and excessive fat and muscle in the feces than when these abnormalities are evident. If diabetes is associated with long-continued bronzing of the skin and enlargement of the liver, in the absence of jaundice and the characteristic distribution of the pigment in Addison's disease the suggestion is direct that chronic fibrous pancreatitis is present. Anschütz has tabulated twenty-four cases of complication since the original publication by Hanot and Chauffard on this subject (the bronzed diabetes of the French writers).

In this paper by Fitz there is a table to show the relation between visible fecal fat, jaundice, and pancreatic disease. Only those cases are included which gave anatomical changes at autopsy, a laparotomy, or by passage of a pancreatic calculus, that there was actual disease of the gland. Without going into the details of figures the table suggests that in about three-fifths of the cases of steatorrhœa attributable to pancreatic disease there is neither diabetes nor jaundice; that in two-fifths there was either diabetes or jaundice in about equal proportions, and in but few instances is there a combination of diabetes and jaundice. In another table the view of Müller is brought out that in pancreatic disease there is less splitting of fat and consequently an increase in the neutral fat, thus giving a satisfactory explanation of the oily stools of older writers. This is not the case without exception, however. The possibility is that the feces may contain an excess of fat not only in cases of jaundice, but also when there is superabundance of fat in the stools, and also when there is an abnormality of the absorptive function within or without the intestinal wall. Steatorrhœa is, therefore, to be regarded as an evidence of disease of the pancreas only when other causes for its presence can be excluded, the most important of which is interference of flow of the bile into the intestine.

Fitz emphasizes that any disturbance in the digestion and assimilation of fat, muscle, and carbohydrates from affections of the pancreas has almost invariably been connected with extensive and protracted lesions. It is obvious, therefore, that feeding with an increased quantity of one or the other of these constituents of diet in suspected cases of pancreatic disease might be followed by appreciable changes in the secretions and excretions earlier than otherwise would have been the case. It is clear, also, that disturbances in the digestion of fats, starches, and proteids, relieved by the addition of the pancreas or its preparations to the diet, provided disease of the digestive glands could be eliminated, might furnish additional evidence in favor of the pancreatic source of the disturbance.

Regarding the dietetic experiment of testing the functions of the pancreas, Fitz agrees with the view of increasing the quantity of fat in the diet nearly to the limit which is to be reached without producing

steatorrhea in healthy persons or in patients not suffering from disease interfering with the absorption of fat. It would be particularly desirable to know the toleration of fat in those cases of diabetes in which the pancreas presents no abnormal condition. These methods require the trained chemist. In a like manner the capacity of the patient for digesting muscle fibre in the intestine as compared with that of a normal individual should be tested. Of course, this would necessitate that we should first know the condition of the gastric function, and that we should introduce into the intestine muscle fibre as free as possible from the influence of gastric digestion.<sup>1</sup> The efficiency of the pancreas for digesting the starches might be tested by an experimental alimentary glycosuria. The salol method of Ewald and Sievers and the glutoid iodoform capsules of Sahli are chemical methods of doubtful efficacy in the diagnosis of pancreatic disease. Opie<sup>2</sup> has suggested the possibility of discovering in the urine the fat-splitting ferment set free in acute pancreatitis. He endeavored to determine its presence in one case by following the method proposed by Kastle and Loevenhardt, which is based upon the decomposition of ethyl butyrate by the ferment and the production of butyric acid. The urine neutralized with potassium hydroxide was divided into two portions, one of which was boiled for the purpose of destroying the ferment. Ethyl butyrate was added to each specimen. That unboiled after twenty-four hours gave an acid reaction, while the boiled specimen showed little if any change.

The symptoms and signs which have proved most useful, according to Fitz, in the diagnosis are those which call attention directly to the region of the pancreas. They are epigastric pain, tenderness, tension, and tumor, with or without obstructive jaundice, and evidence of mechanical interference with the motility of the stomach and duodenum. Although the diagnosis of diseases of the pancreas, in the light of our present knowledge, depends practically more on the symptoms calling attention to the locality of the organ than upon the evidence of disturbance of its function, it is reached eventually by the exclusion of other sources than the pancreas, as causes of the local symptom. Fitz refers to his publication on acute pancreatitis made in 1889, and repeats that the symptoms are essentially those of a peritonitis beginning in the epigastrium, and occurring suddenly during ordinary health without obvious cause. The diagnosis is based on the pain, tenderness, and tympany limited to the region of the pancreas, and on the gradual development of deep-seated peritonitis.

<sup>1</sup> Ground meat pulp might be introduced into the duodenum by Hemmeter's or Kuhn's method of duodenal intubation.

<sup>2</sup> Johns Hopkins Hospital Bulletin, 1902, vol. xiii. p. 117.

The differential diagnosis lies practically between an irritant poison, perforation of the digestive or biliary tracts, and acute intestinal obstruction. In cases of acute pancreatitis thus far reported no new evidence has been furnished which gives to the diagnosis more than a variable degree of probability. Certainty has been reached only by laparotomy or a post-mortem examination. Fortunately, exploratory laparotomy has proved the most satisfactory method of treatment for relief of acute symptoms in an increasing number of cases.

The diagnosis of *chronic* pancreatic affections is based on the occurrence of localized pain and presence of tumor; the evidences of disturbed pancreatic function are to be sought along the lines previously mentioned, but experience has shown that definite and convenient additions to our knowledge are necessary before functional disturbances of the pancreas can be ascertained sufficiently early and with sufficient certainty to render assured the pancreatic source of the disease.

### DISEASES OF THE PERITONEUM.

It is evident that a presentation of diseases of the peritoneum considered from the purely clinical standpoint in a work which will contain presentations from the surgical, gynecological, and purely bacteriological aspects must necessarily be very limited; for if we exclude those forms of peritonitis that are due to infection originating (1) from the gastrointestinal tract (perforations of the stomach and intestine, appendix); (2) peritonitic infections originating from inflammations of the biliary apparatus; (3) and those traceable to infections from the genito-urinary tract (kidneys, uterus, tubes, and ovaries)—all of which are surgical problems—not much is left for the purely internal clinician. One cannot fail to be impressed with the rapid progress that has been made in the recognition and more rational treatment of the various forms of peritonitis, and it is a just desert of especially American surgeons that the most of this progress has been due to their efforts. In a number of the forms of peritonitis due to infection from the sources above mentioned there can be no doubt whatever that the cases belong to the field of the surgeon. This is particularly true of the peritonitis due to perforations of the gastrointestinal tract and cholelithiasis. On the other hand, it must not be claimed, as some ultra-ambitious surgeons would lead us to believe, that the clinician has no occasion to treat peritonitis whatever. One of the ablest surgeons<sup>1</sup> with whose work I am acquainted treats a very large number of his cases of peritonitis by a purely ex-

<sup>1</sup> A. J. Ochsner. Surgical Treatment of Tuberculous Peritonitis. Transactions of American Surgical Association, 1903.



pectant and internal treatment. Even in the treatment of appendicitis Ochsner has become more conservative, and does not operate at once or at any time in all cases. His aim is now to change the acute cases, in which the mortality of operation is greatest, into another class, in which the mortality is very small after operation. This he effects by conservative treatment, involving chiefly gastric lavage, exclusion of food from the mouth, exclusion of cathartics by the mouth, and rest. He advocates quenching the thirst even, by rinsing the mouth with cold water and the use of small enemata.<sup>1</sup>

**Physiology of the Peritoneum on the Protecting Action of the Omentum.** It has long been supposed, on theoretical grounds, that the omentum in some way controls the blood pressure of the abdominal organs, because it is able to take up a very large amount of blood in its spacious blood channels and without suffering any detriment, which must necessarily occur if the same engorgement had to take place in one of the abdominal organs. De Renzi<sup>2</sup> described the results of his experiments, which tend to prove that the omentum plays an important rôle in maintaining the activity of the circulation of the abdominal organs, particularly that of the spleen.

**Septic Thrombosis of the Roots of the Portal Vein and of Pyléphlebitis** is of interest. A paper on this subject has recently been published in American literature by Arpad A. Gerster,<sup>3</sup> of New York. This paper will no doubt stimulate pathologists to examine cases that have been operated for peritoneal sepsis traceable to any causes mentioned at the beginning of this chapter for evidence of the infection and thrombosis of the portal vein. Gerster goes very extensively into the literature of peritoneal sepsis in relation to this question. The important points in the diagnosis as emphasized are the following: 1. Presence of precedence of the infection involving the abdominal organs. 2. Presence of pyæmia. 3. Implication of the liver. The prognosis, while stated as being very grave, is not always hopeless, but the only safeguards are early diagnosis and prompt operation.

An intensely interesting paper bearing on the peritonitis caused by the entrance of gastric contents is published by Conrad Brunner.<sup>4</sup> Brunner brought the gastric contents gained by aspiration from the stomach into the abdominal cavity of guinea-pigs. He found that small quantities of gastric juice with normal percentage of HCl did not kill the rabbits, but if the HCl was absent all of the animals infected

<sup>1</sup> Mortality in Appendicitis; Its Cause and Limitation. Medical News, May 2, 1903.

<sup>2</sup> La semaine médicale, November, 1902.

<sup>3</sup> Reported to the American Surgical Association, in Washington, May 12, 1903. New York Medical Record, June 27, 1903, p. 1005.

<sup>4</sup> Archiv f. klin. Chir., Band lxxvii. p. 804.



died of peritonitis. These results show that the percentage of HCl in the gastric juice is capable of diminishing the virulence of the microbes causing peritonitis, and therefore the peritonitis occurring from entrance of small quantities of gastric contents into the peritoneum during operations for carcinoma of the stomach must have a high degree of virulence. In perforation from gastric ulcer the gastric contents are much less infectious, varying according to the time that the chyme was exposed to the HCl digestion. In another series of experiments he tested the effect of washing out the peritoneal cavity with normal salt solutions for peritonitis. It was found that infected animals that were washed out in this way lived five days longer than the control animals. The experiments demonstrated that the resistance of the human peritoneum is greater than that of the animals experimented upon.

**Peritonitis Treated by Alcohol Applications.** Ssaweljew<sup>1</sup> reports two cases of peritonitis treated by external application of alcohol. The first was a case due to perforated gastric ulcer, and the second due to a perforation from appendicitis, and the typical symptoms of perforation from these two causes are given. The alcohol was applied in the following manner: A soft napkin was folded together four times, soaked in alcohol, and when there was no more dripping from it the entire abdomen was covered with it. Parchment paper was covered over the napkin, and the edges of the parchment tucked underneath the napkin on all sides so as to prevent wetting of the clothes of the patient. In the beginning he did not even use the parchment paper, because of the terrible pains, which even the weight of the parchment paper seemed to increase. The applications were made every half-hour, then at longer intervals; finally, only twice in every twenty-four hours. Improvement followed on the second day. Both cases were cured. The author offers several theories in explanation of the action of alcohol; for instance, that by cooling, that by virtue of the hygroscopic action. Some writers claim that alcohol might be absorbed through the skin and act antiseptically upon the peritoneum. Some assume that the alcohol works as a derivative or counterirritant. Finally, the theory of hæmotaxis has been drawn in explanation of this action, on the assumption that the alcohol causes an accumulation of phagocytes and thereby antagonizes the inflammatory process.

**Bacteriology of the Fibrinous Exudate in Septic Peritonitis.** Thomas J. Lanahan<sup>2</sup> reports his studies on this subject. In 1897 John M. T. Finney<sup>3</sup> advocated that the flakes of partially organized lymph should be thoroughly wiped off of the intestine during lapar-

<sup>1</sup> Alkoholumschläge. Allg. med. Centralblatt-Zeitung, Nos. 12, 13.

<sup>2</sup> Journal of Medical Research, June, 1903.

<sup>3</sup> Johns Hopkins Hospital Bulletin, 1897.

otomies for peritonitis, and asserted that the success of the operation depended upon this method. From the experiments of Lanahan referred to it is to be concluded that in most cases of peritonitis with fibrinous exudation bacteria are present in large numbers in the fibrin. This would justify the removal of the exudate as a safeguard against further infection after the operation.

**Peritonitis without Perforation in Typhoid Fever.** J. L. Yates<sup>1</sup> conclusions are :

1. Non-perforative peritonitis usually results from an extension of inflammation through the basis of deep intestinal ulcers, but may also arise from the migration of bacteria through an intestinal wall which is relatively but slightly abnormal.

2. Meteorism predisposes to an infection of the peritoneal cavity, and by decreasing the normal peritoneal absorption furnishes a secondary cause for peritonitis.

3. A hæmatogenous origin of peritonitis is possible in typhoid fever.

4. Non-perforative peritonitis is commonly caused by the typhoid bacillus, and the resulting inflammation is usually diffuse and often severe.

5. The inception of such a peritonitis is clinically indistinguishable from the so-called signs of perforation, and the symptoms in both are due to peritoneal inflammation. The prognosis is probably equally grave in the two forms.

6. There should be appropriate surgical intervention immediately the peritonitis can be recognized.

7. Thrombi, and among them those composed of agglutinated red blood corpuscles, may lead to hemorrhages into the wall of the intestine, and the resulting changes favor the transmigration of bacteria into the peritoneal cavity.

8. Infarction of the spleen may have a similar thrombotic causation, but simple splenic infection is probably not a cause of peritonitis.

9. The specific action upon human blood of an agglutinin generated by the typhoid bacillus can be demonstrated in vitro.

In connection with the purely *medical treatment of peritonitis*, especially that by external applications on the abdomen, it is of interest to present the observations of Prof. Baginski.<sup>1</sup> Baginski and Prof. Senator presented three children to the Medical Society of Berlin who had suffered from chronic peritonitis and had been cured simply by rubbing soft green soap into the abdominal integument (*Schmierseife*). Baginski warns against hasty surgical interference, and advocates this treatment with green soap. Senator has replaced the green soap by adding to it vaselin and iodoform. The report of such conservative and able clinicians

<sup>1</sup> American Medicine, May 2, 1903.

<sup>2</sup> Deutsche Praxis, 1902, No. 4.

as Baginski and Senator should cause an investigation into this subject and critical testing as to whether or not such external applications as alcohol, green soap, and iodoform can really bring about a cure of some forms of peritonitis. The first thing to do is to establish that this cure can be accomplished in the manner described. Investigations to solve how will follow afterward. Prof. Comby,<sup>1</sup> of Paris, treats tuberculous peritonitis by rest, fresh air, highly nutritious and digestible diet, and inunction of the abdomen with iodine and green soap. Instead of giving creosote internally, as Comby recommends for peritonitis, Winternitz<sup>2</sup> urges thyokol, which can accomplish everything that creosote can do, but at the same time it is non-irritating, non-toxic, and odorless. The dose is from 0.5 gm. to 1 gm. (7.5 gr. to 15 gr.) three to four times daily. It has a bitter taste, and should be given in wafers or in form of syrup.

THAT TUBERCULOUS PERITONITIS may heal spontaneously is demonstrated by the observations of O. Borchgrevink,<sup>3</sup> who reports the case of a girl, aged sixteen years, who had passed through an attack of pericarditis, from which she recovered very slowly. Shortly after this she developed an abdominal effusion; she was tapped, eleven litres of a yellowish-green fluid being drained off. The effusion reaccumulated rapidly, but later disappeared completely without any special treatment. The tuberculous character of the fluid was demonstrated by inoculation of two guinea-pigs, both of which died of general tuberculosis. Several years after the patient died suddenly after a short illness. The autopsy revealed a tuberculous pleurisy and pericarditis; both of these were probably secondary to a tuberculous lymphatic gland in the neighborhood; there was a typical chronic peritonitis, but at no place in the abdominal cavity could any tubercles be found either by macroscopic or microscopic examination. The only signs of a previous tuberculosis of the peritoneal cavity were the thickened peritoneum and dense adhesions. A few tubercles were found in the tubes and the uterus. This case teaches us that tubercles developing on serous membrane may disappear completely, and that tuberculous peritonitis may heal spontaneously at times and without laparotomy or other operative interference.

It is difficult to conjecture what the result might have been in this case if the other organs had been normal, but it demonstrates the possibility of a cure of tuberculous peritonitis. If there is one deduction justifiable from the literature of the past year on peritonitis it is that the treatment of it is becoming more conservative, and that even leading surgeons are willing to make use of the expectant plan in certain well-defined forms of this disease.

<sup>1</sup> Münchener med. Wochenschrift, 1902, No. 40.

<sup>2</sup> Deutsche Aerzte Zeitung, 1902, H. 1.

<sup>3</sup> Deutsche med. Wochenschrift, January 15, 1903.



graduated at Cambridge in 1841, in the same year was elected a fellow of Pembroke College, and was elected Lucasian professor of mathematics at Cambridge in 1849. In 1885 he became president of the Royal Society, and from 1887 to 1892 was member of Parliament for Cambridge University. He was made a baronet in 1889, and in 1902 became master of Pembroke College. He was distinguished as an expounder of the principles of hydrodynamics, of spectrum analysis, and of the phenomena of fluorescence and phosphorescence, and his publications include the 'Burnet Lectures on Light' (1892); 'Mathematical and Physical Papers' (1880-1902); 'Gifford Lectures on Natural Theology' (1891-3); and many papers printed in the transactions of learned societies.

**Stokes, Whitley**, Irish Celtic scholar: b. Dublin 28 Feb. 1830. He was educated at Trinity College, Dublin, and called to the bar at the Inner Temple in 1855. He went to India in 1862, and became successively secretary to the governor-general's legislative council and to the legislative department of the government of India. In 1877-82 he was law member of the governor-general's council, and during his official career in India drafted the greater part of the present codes of civil and criminal procedure as well as numerous acts relating to property, trusts, etc. In 1879 he was president of the Indian Law Commission. In 1868 he proposed a scheme for collecting and cataloguing the Sanskrit manuscripts preserved in India. His published works include those treating of legal, and those dealing with Celtic subjects. The former comprise 'Treatise on the Liens of Legal Practitioners' (1860); 'On Powers of Attorney' (1861); 'Hindu Law Books' (1865); 'The Older Statutes in Force in India, with Notes' (1874); and 'The Anglo-Indian Codes' (1887-8; supplements, 1889-91); etc. Among his Celtic works may be named 'Irish Glosses' (1860); 'Three Irish Glossaries' (1862); 'The Play of the Sacrament' (1862); 'The Passion, a Middle Cornish Poem' (1862); 'The Creation of the World, a Cornish Mystery' (1863); 'Three Middle Irish Homilies' (1871); 'The Tripartite Life of St. Patrick' (1887), in the Rolls Series; 'Lives of Saints from the Book of Lismore' (1889); 'Urkeltscher Sprachschatz' (1894), with Bezenberger; 'The Annals of Tigernach' (1897); 'The Eulogy of St. Columba' (1899). He is joint-editor of 'Irische Texte' and of the 'Archiv für Celtische Lexikographie.'

**Sto'la**, the Latin name of a loose garment worn by Roman matrons over the tunic. To the bottom of it a border or flounce was sewed, the whole reaching down so low as to conceal the ankles and part of the feet. It was the characteristic dress of the Roman matrons, as the toga was of the men; divorced women or courtesans were not allowed to wear it. It was usually gathered and confined at the waist by a girdle, and frequently ornamented at the throat by a colored border. It had either short or long sleeves, and was fastened over the shoulder by a fibula.

**Stolberg, stöl'berg, Christian**, German author: b. Hamburg 1748; d. 1821. He traveled through Switzerland and North Italy in company with Goethe and Lavater; settled in Schles-

wig, and wrote poems, dramas, etc., besides a translation of Sophocles and other works from the Greek. He was influenced by Klopstock.

**Stolberg, Friedrich Leopold**, German poet: b. Hamburg 1750; d. 1819. He wrote plays, poems, travels, etc.; translated the 'Iliad,' four tragedies of Æschylus, some of the works of Plato, and Ossian's works. In 1800 he joined the Roman Catholic Church, after which he wrote an elaborate 'History of the Religion of Jesus Christ.'

**Stole**, a long narrow band or scarf with fringed ends, worn by ecclesiastics of the Roman Catholic and Protestant Episcopal churches, by deacons over the left shoulder, being fastened under the right arm; by bishops round the neck with both ends pendent in front to the knees; and by priests similarly, but with the ends crossed over the breast at mass.

**Stolp, stölp, or Stolpe, stöl'pē**, Germany, in Prussia, in the province of Pomerania, on the river of its own name, 64 miles west of Dantzic. The interesting features are a castle of the 16th century, two good churches, and the ancient town-gates, besides several schools. The industries are chiefly fishing, iron-founding, linen-weaving, and amber-turning. There is some trade in cattle, fish, geese, grain, and liquor. The port is Stolpmünde at the mouth of the river—this is also a favorite summer resort. It formerly belonged to the Hanseatic League. Pop. (1900) 27,272.

**Stomach.** The ancients conceived digestion (q.v.) as a process of cooking, executed by the animal heat of the body. Not until the 17th century was the idea advanced that digestion in the stomach was a chemical process largely due to ferments. In 1752 Réaumur, and in 1783 Spallanzani, established that the main factor in digestion was a secretion of the stomach, the gastric juice, which dissolved and transformed the ingested food-stuffs chemically. Previous to that time—even in the 17th century—digestion was thought to be due to a mechanical trituration of the food. Réaumur knew that the secretion of the stomach was acid, but it was not until 1834 that Prout discovered that the acidity was due to hydrochloric acid (HCl). In 1836 Schwann recognized the active ferment of the gastric juice, the pepsin.

A research work of the most far-reaching importance concerning the nature of stomach digestion was executed by the American military surgeon, William Beaumont on the stomach of the Canadian hunter, Alexis St. Martin. After a gunshot wound had opened the organ, it healed not perfectly but, leaving a fistula permitting introspection and direct, objective study of digestion. The investigations of Beaumont constitute what may justly be designated as the most epoch-making research on the physiology of the human stomach. ('Experiments and Observations on the Gastric Juice and the Physiology of Digestion,' 1833.)

The digestive processes in the intestines were first systematically studied by Claud Bernard, who discovered in 1848 that the pancreatic juice digested fats. Corvoisart in 1857 discovered the albumen-digesting power of the pancreatic juice. In 1865 the secretion of the intestinal glands was gained in a pure state by Thiry. Valuable contributions to the physiology of di-



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gestion in the stomach and intestines have been made by J. P. Pawlow, of the Institute for Experimental Medicine, Saint Petersburg. These scholarly researches belong to the most recent acquisitions to our knowledge of the digestive tract. Still much remains to be worked out. Even at the present time the function of the bile is not understood, nor are the functions of the liver and pancreas satisfactorily investigated. In a brief and practical account like this, the reader seeks only well-ascertained facts, and not hypotheses. What he wants to know is (1) how the stomach works under healthy conditions, what are its normal performances, and (2) how its abnormal conditions are brought about, how its diseases are manifested, and what are the best means of avoiding or curing them.

*Normal Gastric Digestion.*—For an understanding of the normal functions of the stomach, a brief reference to recent discoveries is indispensable. The stomach is not the main digestive organ, only one seventh of the entire digestive process occurs in it. The remaining six sevenths of digestion are carried on in the intestines. But it would be a grave error to assume for this reason that the stomach is not necessary for the digestive process. For so dependent is intestinal digestion upon gastric digestion that it is impossible to have a normal digestion in the intestines without a previous digestion in the stomach. It is also a mistake to assume that the intestinal digestion is normal in individuals who for surgical reasons have had to undergo the operation of the removal of the stomach as a whole or in part. None of such operated cases have lived over a year or six months, although they were kept under constant supervision and the most careful dietetic control.

The chemical changes which the various food-articles undergo in the stomach are of far-reaching importance for the changes which are to occur in these foods after they reach the intestines. Many of the old authors, beginning with the American physiologist, Beaumont, believe that the mechanical irritation of the foods causes the gastric secretion, but the experiments in Pawlow's laboratory have proved the fallacy of this view. In the first place, if the secretion were due to simple mechanical irritation, there is no reason why irritation with the point of a glass rod, with a feather, or with sand placed in the stomach, should not also cause the secretion. A secretion may be caused by mechanical irritation, but it is composed mainly of a liquid resembling plasma, containing mucus, and having no digestive power. The mistake of the older experimenters, according to Pawlow, grew out of the fact that they ignored the so-called psychic secretion, a secretion which can be set up by the mere smell of food, or even by a very intense feeling of hunger. If the œsophagus of a dog be cut, and its end sewed to the edges of an abdominal wound, and at the same time a gastric fistula be established, pieces of meat which are fed to the dog after healing of these fistulae will not reach the stomach, but will fall out of the upper end of the fistula leading into the œsophagus. Nevertheless in five to six minutes after the swallowing of the food gastric juice begins to be secreted, running from the gastric canula first in drops and afterward in a continuous stream. If the dog be offered meat without receiving it, the gastric secretion will also appear,

though not so plentifully as when the dog was actually allowed to eat the meat. A further interesting fact observed in dogs so experimented on was that no secretion followed the swallowing of indigestible substances like small stones. These experiments furthermore elicited the astounding fact that for every kind of food a definite gastric secretion is formed of specific composition. Therefore it may be said that the stomach provides a special gastric juice to meet each dietetic requirement. It must therefore be concluded that the mucous membrane of the stomach is capable of distinguishing between the varieties and classes of foods that come in contact with it, much as the skin recognizes mechanical, chemical, thermic, and electrical stimulation. It might be asked, "What is the object of this psychic secretion?" for Pawlow has clearly established the existence of two kinds of gastric secretion, the chemic and the psychic. This question applied to the human physiology would be the same as inquiring, "What is the object of the appetite?" The answer is, that under the influence of the psychic secretion a gastric juice is furnished which is much more effective than that which is secreted under purely chemical stimulation of the food, that is, when food is taken without any special appetite. Furthermore, under the influence of psychic secretion foods which would otherwise not stimulate the gastric mucosa to secretion become converted by the already present psychic secretion into something else which constitutes a further stimulant to the secretion of gastric juice. For instance, if a solution of albumen be administered to a dog upon which a Pawlow operation has been performed, that is, splitting off part of the stomach, with all the vessels and nerves intact, and making this second smaller stomach communicate with the abdominal wall, but not with the general cavity of the large stomach from which it is dissected (see 'International Clinics,' Series XII., Vol. II., p. 276) there will be no secretion from the small stomach, for albumen by itself does not excite chemical secretion. But if the psychic secretion is previously set up by some other means, before the albumen is placed in the large stomach—for instance, by waving a piece of meat before the dog's eyes—then, following the introduction of albumen, a secretion will be found in the small (artificial) stomach which is qualitatively and quantitatively greater than the psychic secretion alone, or when albumen is given alone, it is evident that, while albumen in itself does not excite secretion, the products of albumen do cause this secretion. The same is true of pieces of bread which, when placed in the large stomach through the fistula, will not promote a secretion; but if the dog is allowed to swallow the bread, secretion begins and continues for several hours. Psychic secretion therefore is a preparatory secretion, transforming substances, which otherwise would not stimulate the stomach into such conditions as can accomplish this stimulation. The fact that bread will cause a secretion when chewed and swallowed, and not when placed directly in the stomach through the fistula, may be interpreted (as by Pawlow and Peter Borisoff) as proving the secretion of a gastric juice under psychic influence; but—as will be shown presently—it may be due to a special body in the saliva that stimulates gastric secretion.

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Further revelations from Pawlow's laboratory disclose very important relations between the various classes of food, permitting the conclusion that they may mutually advance or interfere with the digestion of their various constituents in the gastric chyme. For instance, starch paste does not by itself promote gastric secretion, but when mixed with meat it was found to accelerate the action of the gastric juice, increasing its digestive power. Furthermore, it was demonstrated that the stomach is capable of

it. The name of "salivary secretin" has been proposed for this body, which appears also to be a normal stimulant for the gastric glands.

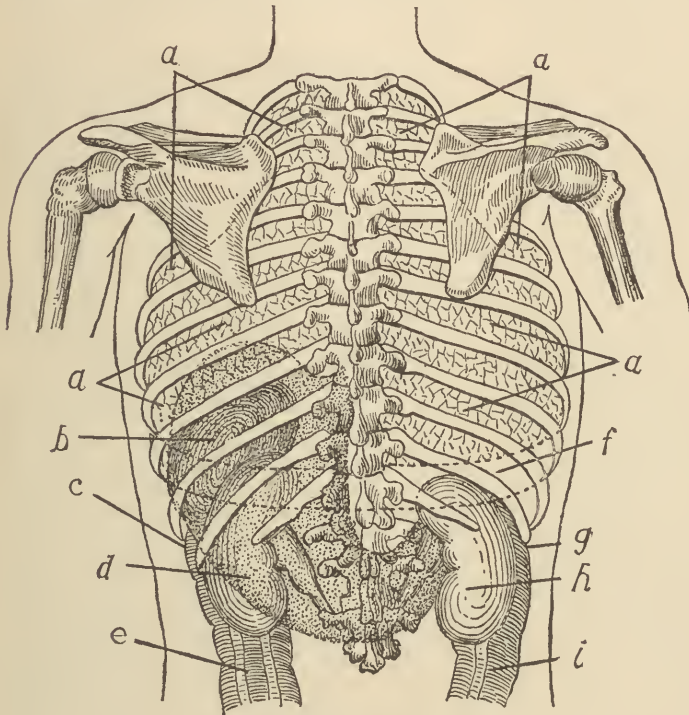
The human stomach accomplishes its work by the means of three essential functions, secretion, absorption, and peristalsis (this term refers to the movements of the stomach). The secretion of the gastric glands owes its digestive power to hydrochloric acid and four ferments. The quantity of hydrochloric acid amounts to two parts in the 1,000 of gastric juice. The

ferments are pepsin, which acts mainly on the proteid constituents of food like meat and egg, rennin or chymosin, which acts principally upon milk, precipitating the casein; lipase, which is a fat-digesting ferment; and the new gastric ferment, "chymaze," which is not a digestant of food, but an accelerator of the digesting action of the ferments of the pancreatic juice. (International Clinics, Vol. II., 12th Series, p. 276, article by Peter Borisof).

*Dependence of Intestinal upon Gastric Digestion.*—It is a prevalent opinion among the laity that the stomach has a marked absorptive power. This is a natural consequence of an older error, according to which the stomach is the chief digestive organ, it having been formerly believed that by far the greater part of the digestive act takes place in the stomach. As already intimated, the actual digestion which takes place in the stomach is insignificant compared with that which takes place in the

intestine. Later it will be shown here that the secretion of pancreatic juice depends upon the liberation from the membrane of the duodenum, or first part of the bowel, of an agent called *duodenal secretin* (discovered by Bayliss and Starling), and that the liberation and secretion of this agent depends upon the presence of hydrochloric acid in the gastric chyme. So that if this acid is not present in the chyme as it enters the upper bowel, there can be no normal performance of intestinal digestion. Just as normal gastric digestion depends upon a normal condition of the mouth and normal salivary secretion, so normal intestinal digestion depends upon a normal stomach.

*Absorption from the Stomach.*—The amount of absorption that takes place from the stomach is surprisingly small. Water is practically not absorbed at all, for it appears that fully 95 per cent of all water taken into the stomach is passed out into the duodenum and absorbed from the intestine. Alcohol and substances in



DORSAL VIEW.

(Dotted area shows location of Stomach.)

- |                     |                         |                     |
|---------------------|-------------------------|---------------------|
| a. Lungs.           | d. Left kidney.         | g. Hepatic flexure. |
| b. Spleen.          | e. Descending colon.    | h. Right kidney.    |
| c. Splenic flexure. | f. Complementary space. | i. Ascending colon. |

distinguishing between lactic, butyric, and hydrochloric acids, and responded to each of these acids with a varying quantitative secretion. As lactic and butyric acids are products of gastric fermentation, their stimulating influence on gastric secretion is of therapeutic importance. It is evident, therefore, not only that the stomach is extremely delicate in detecting the composition of foods and regulating the composition of its secretion correspondingly, but that it can distinguish between various organic acids. These experiments furthermore gave the clue to the treatment of gastric secretory disorders not by drugs merely, but by dietetic measures.

The writer has discovered in normal saliva a body which, if added to digesting mixtures of gastric juice, accelerates the digestive power of the gastric secretion. In other words, this new salivary constituent will effect a more rapid conversion of proteid into the albumoses and peptones, a quicker solution of boiled-egg albumen, and of fibrin, than would occur without



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solution of alcohol are readily absorbed. Grape, milk, cane-sugar, and maltose are absorbed in moderate amounts when they are in aqueous solution. When they are in alcoholic solution larger amounts are absorbed. Dextrin and peptones are also taken up from the stomach, but in smaller amounts than sugar. The amount of these substances absorbed increases with the concentration of the solution. But simultaneously with this absorption occurs a more or less active secretion of water into the stomach, which secretion increases or diminishes directly in proportion to the amounts of the substances absorbed. So that under certain conditions it is possible to draw more water out of the stomach by means of a stomach-tube than has been drunk half an hour previously, which certainly refutes the assumption that water could be absorbed from the stomach, and favors the view that water is not only not absorbed, but that it is actually secreted into the stomach under certain conditions. This conclusion is of great value in the treatment of certain dyspepsias characterized by a weakened condition of the gastric musculature; for in these the contractile power of the stomach is not sufficient to expel the water into the bowel at the proper time. And as water is, bulk for bulk, the heaviest substance which the human being takes into the stomach, its retention in the stomach beyond a certain length of time drags down and exhausts the already attenuated gastric muscle and dilutes the already weakened gastric secretion. Therefore in some forms of gastric atony an essential part of the treatment consists in restricting the amount of water to the lowest possible requisite, and to give it by means of colon-injections, if necessary, for a time at least; or if some of it must be taken by way of mouth, to induce the patient to lie on his right side and by means of massage to facilitate the expulsion of the water from the stomach into the intestine.

*The Gastric Peristalsis or Motor Function of the Stomach.*—This is perhaps the most important function of the stomach, for not only does the motor function mix and churn up the gastric contents, but it expels them at the proper time into the bowels. An animal might live without a gastric secretion, or with a stomach which could not absorb anything, but it could not live with a stomach that had no peristalsis. The muscular layer of the stomach is much thicker and stronger at the pyloric end, which is near the outlet toward the intestine, than at the cardiac end, which is the dilated rounded pouch extending in the opposite direction. The cardiac end of the stomach is therefore very quiet during the digestive act, and the principal gastric movements of churning and expulsion occur in the pyloric end where the muscles are strongest. According to Oppel, the cardiac or quiet end of the stomach in certain animals, like the horse, pig, and rat, is functionally distinct from the pyloric end. It is lined by a different kind of epithelium called pavement epithelium, and its glands have no acid secretion. Accordingly this quiet region is, even under normal conditions, the seat of active starch digestion. It has been thought that, inasmuch as the starch-converting agency of the saliva could not act in the presence of an acid like that of the gastric secretion, therefore all starch digestion was ar-

rested in the stomach, and was not resumed until the food reached the intestine. That this is not the case is shown by W. B. Cannon, who proved that in man as in other animals the cardiac end of the stomach serves chiefly for starch digestion by the action of the salivary ptyalin during the early part of digestion in the stomach. ('*American Journal of Physiology*,' Vol. VI., p. 396.) This again emphasizes the importance of thorough mastication, for only thereby can the food be thoroughly penetrated by the saliva, and further starch conversion take place in the cardiac end of the stomach during gastric digestion.

The movements which food undergoes in the stomach during digestion can be studied by the aid of the X-rays. An inert and insoluble substance which is capable of cutting off the X-rays must be mixed with the food in order to make the gastric movements visible before the Roentgen apparatus. Bismuth subnitrate answers this purpose admirably. Even the movements of the human stomach can be studied by adding this insoluble substance to the food, and placing the individual who has eaten it before the X-ray instrument. In this way it has been discovered that the pyloric or highly muscular portion of the stomach is the part where the most effective gastric movements are brought about. The movements in the other portions of the stomach are not of sufficient force to be noticeable before the X-ray apparatus. It seems probable therefore that the fundus or pouch end of the stomach serves simply to push the food into the pyloric end, where it is shot to and fro for a while, and eventually expelled into the duodenum. Three or four inches from the exit of the stomach, known as the pylorus, the musculature of the stomach is particularly strongly developed (sphincter muscle of the centrum pylori); and here it is that the stomach may constrict to such an extent as to partition off a special portion of the pyloric end and expel the food into the duodenum without permitting of any regurgitation into the fundic end. All this is in contradiction of the view originally held by Beaumont, and still adopted in some of the most recent text-books of physiology, that there is a regular circuit of the food around the walls of the gastric cavity.

*Structure of the Stomach.*—It is impossible to enter here into a consideration of the microscopic structure of the stomach, although this is indispensable for the proper understanding of its abnormal functioning. Much is yet to be learned concerning the cells of the peptic glands and their function. It is certain, however, that the different products of the gastric secretion, the hydrochloric acid and the ferments, do not originate in the same cells, but that there are acid-producing cells and ferment-producing cells in the glands within the stomach. It is even probable that the different ferments of the stomach are produced by different cells. The organ is composed of five different coats. Passing from without inward, these are: (1) the peritoneal; (2) the muscular coat, which is in turn composed of the longitudinal and circular layers; (3) a connective tissue layer; (4) a very small thin layer of muscular tissue, called the muscularis mucosæ, separating the connective tissue from the glandular layer; (5) the glandular layer itself, innermost of all. In addition

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to these structures the stomach is permeated by arteries and veins, a liberal network of lymphatics, and is richly supplied with nerves.

*The Abnormal Digestion of the Stomach; Gastric Diseases.*—One of the first and most important things to decide when an individual complains of dyspepsia, or of any distress, pain, distention, or symptom referable to the stomach, is whether the signs and symptoms are really traceable to the stomach or not. For one may have all the symptoms of gastric disease, and yet the stomach itself may not be abnormal either in structure or function. For instance, the stomach may give rise to abnormal sensations as a consequence of disease of other organs. The organs which most frequently derange the stomach in this manner are the heart, liver, and kidneys. Even physicians of experience who have become afflicted with abnormal gastric digestion have been at times deceived concerning the true source of their malady. Fully two thirds of all gastric sufferers who come to special clinics devoted to diseases of the stomach are suffering not from any primary disease of the stomach whatever, but either from a nervous affection of the stomach or from one of the gastric derangements that are secondary to disease of other organs. Perhaps the most frequent of these disorders are those that are due to the nervous gastric affections, or as they are called, the *gastric neuroses*. To determine precisely the exact nature of an affection of the stomach, the chemical analysis and microscopic examination of known test-meals is indispensable. According to the gravity of the morbid condition, a heavy or a light test-meal is given, and a certain time after it is eaten the stomach-tube is passed into the stomach, and a certain amount of the gastric contents withdrawn for analysis. As long as this is not done, all deductions from the symptoms and signs alone are conjectural. I do not mean to say that the inferences drawn from test-meal analysis and microscopical examination of test-meals are always conclusive. It is frequently necessary to examine also the blood and the urine of the patient, and even to examine the stools after certain test-meals. Then all the other organs of the body should be carefully examined, bearing in mind that it is not always correct to presume that a patient has a disease of his stomach because he has gastric symptoms. The reverse is equally true, that a patient may have no symptoms whatever referring to the stomach, and yet have very grave disease of this organ. The gravest affection which may befall the organ—cancer of the stomach—has been known to run its entire course and cause death in a latent manner; that is, without giving a single symptom referable to the stomach. This is an instance where a patient may have a gastric disease and no gastric symptom. A person who suffered from almost complete blindness, yet manifested no disease in his eyes, was found after some study to have been thus affected by poison circulating in his blood, which was absorbed from his gastro-intestinal canal, and was due to an abnormal digestion. Under treatment directed toward his stomach and intestine his vision gradually returned.

It is important to avoid aggravating an existing trouble by illogical and promiscuous medication, faulty diet, and the use of alcoholic

stimulants. Between 80 and 90 per cent of the so-called stomach tonics, liver regulators, and stomach bitters are composed of alcohol. But even the prescriptions of physicians are not always adapted to the existing conditions. One of the most frequent abuses among practitioners of medicine is the indiscriminate dosing with mixtures containing pepsin. In a similar manner the ferments which convert the starches, the carbohydrates, into sugar, have been much abused. These substances are called *diastases*. Now diastase is a ferment with which the digestive tract is abundantly supplied. It exists in the saliva in the shape of a ferment called *ptyalin*, and in many hundreds of tests with human saliva it has not been discovered in a single case that this substance was not secreted in sufficient quantity. It is conceivable, however, that in a mouth which has been made offensive by carious teeth, by a badly coated tongue, enlarged tonsils, and catarrh of the mouth, throat, and nose, this ptyalin can be destroyed and rendered ineffective. The proper thing to do then is not to give ptyalin or diastase in form of a medicine, but to cure the abnormal condition of the mouth. A frequent form of gastric disturbance is called by general practitioners "amylaceous dyspepsia," which is an objectionable name given to the symptoms of hyperacidity and hypersecretion. This disease is frequently treated by cutting off the carbohydrates or starchy foods, which is irrational, because they cannot be dispensed with, not on account of the starch only, but on account of the proteid which amylaceous foods contain. It will be found from the army rations of men under service of various nations, that the carbohydrate portion of the foods is increased with harder work much more than the proteid or fat portion. Therefore these foods should not be taken away because they may not be perfectly digested; but the cause of the indigestion should, if possible, be removed. If possible, a large amount of natural saliva should be swallowed after meals. Often it has been observed that with the simple supply of additional saliva caused by chewing a piece of rubber, etc., starch indigestion could not be demonstrated in the test-meal, although it had existed before. To Fothergill is attributed the saying that "ferments are crutches." No doubt many an invalid would prefer walking on crutches rather than not at all. But there are many crutch-walkers who, by modern surgery, have been enabled to throw away the crutches and walk unaided. So with the digestive ferments; they may be used with success temporarily, but the best thing to do is to discover how the patient may digest without them. And in case of amylaceous dyspepsia this is accomplished by cure of the excess of hydrochloric acid formation, or restoring the lost motor function of the stomach. For when the starchy foods are retained in the stomach overtime, they are very apt to cause an excessive secretion, or to produce an excessive amount of organic acid by fermenting in the stomach under the influence of bacteria.

*Instruction in Cooking Needed in American Schools.*—One of the chief features in the treatment and also in the prevention of diseases of the stomach is then avoidance of improper medication and, what is even more important, of unsuitable diet. Much improvement is needed



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in American cooking, and public kitchens and cooking-schools might be of great benefit. Serious injury is being caused by insufficient or improper food. Instruction in cooking and diet should be given in all public schools where young girls attend. For nine out of ten girls that attend these schools it will be a greater blessing, and they personally will prove a greater blessing to the community, if they know how to prepare a roast, boil potatoes and make an omelet, than if, ignorant in these things, they can give the most scholarly translation of Vergil. In Germany it is not considered below the dignity of daughters of the highest families, even those directly connected with royalty, to attend cooking schools. Nor is such an education incompatible with the best scientific and classical training. So the prevention of diseases of the stomach demands a wider and more thorough knowledge of the art of cooking. In addition to this, it necessitates a simpler life, closer adherence to the laws of nature, more freedom from business strain and nervous tension, and above all things the avoidance of excess in the use of alcoholic beverages and tobacco. Patients should be impressed with the fact that neither drugs nor any methods of treatment can improve them if they persist in their bad habits and faulty diet. Particularly must American business men, who, with admirable energy, but with little regard for their own health, persist in work too severe for their mental and physical constitutions, be taught

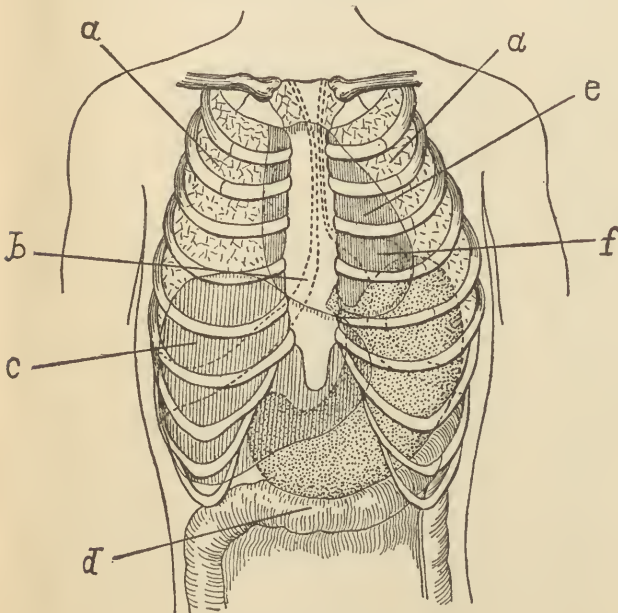
pation. This should in all cases of dyspepsia receive proper attention. When a person begins to feel distress after eating, or eructates, vomits, or has feelings of oppression, fulness or pain in the abdomen and headaches, one of the first treatments that is usually given by sympathizing friends is a drink of some alcoholic beverage, usually whiskey; then comes the abuse of pepsin; very frequently the abuse of some combination containing soda and mint, or some widely advertised panacea for the diseases of digestion. All this is generally being done in the entire absence of a correct recognition of the real disease. The safest thing for the patient to do in the absence of a logical diagnosis is to rest the stomach absolutely for 24 to 48 hours, and not take any food or medicine whatsoever; and thereafter, beginning with the very simplest kind of food—a small plate of farina, of strained oatmeal, a piece of toast, and a cup of hot milk and lime-water—proceed gradually to a cup of bouillon, and a small slice of lean boiled beef. Alcohol, sugars, rich and fatty substances should be avoided for some time.

*Organic Diseases of the Stomach.*—These are the various forms of gastritis (catarrh of stomach, ulcer, carcinoma, etc.) and the displacements and enlargements, dilatation. Displacements—gastropexia—may be congenital or acquired. When the stomach is displaced from its normal position, the condition is in the great majority of cases accompanied with an infirmity of the general nervous system known as neurasthenia (q.v.). Stiller has pointed out that this condition in over 80 per cent of these cases is attended by the loose or floating tenth rib. Normally the tenth rib is attached to the costal cartilages, and these to the breast-bone. But whenever the stomach is displaced out of its normal position and a very diffused splashing sound is audible over the abdomen on shaking the stomach, there is, as a rule, a very movable or floating tenth rib.

Dilatations of the stomach may be primary, due to disease of the structure of the gastric walls. In these cases there is, as a rule, no mechanical interference at the outlet of the stomach, or such interferences are secondary to some obstruction at the outlet. The causes of this obstruction may be scars from old gastric ulcers; tumors, especially cancers; indurative chronic gastritis; or any peritonitic inflammation which may constrict the stomach from the outside. Frequently gall-stones which result in pericyclic inflammation may constrict the part of the bowel immediately below the stomach in such a manner that it is indistinguishable from an obstruction of the pylorus. Five such cases are recently reported in 'Progressive Medicine,' by Prof J. C. Hemmeter,

December 1903, p. 45. So the cause of a dilated stomach is not always to be sought within the stomach itself.

A knowledge of displacements and dilatations of the stomach necessarily precludes a knowledge of its normal position. This is admirably



ANTERIOR VIEW.

(Dotted area shows location of Stomach.)

a. Lungs; b. Complementary pleural space; c. Liver; d. Transverse colon; e. Heart; f. Complementary pleural space.

that the prime factor in their successful treatment is rest. To such cases mental and physical rest is more essential to recovery than medicine or treatment directed to the stomach. Another factor which frequently leads up to stomach diseases is inactivity of the intestines, or consti-

depicted in the accompanying illustrations where it is seen that the larger end of the stomach, or the blind pouch, may extend higher than the fifth rib, on the left side, thus reaching up behind the apex of the heart. This readily explains the distress felt about the heart, and also the irritable heart-action in some forms of gastric disturbance. The anterior view of this illustration also shows the correct or normal relations of the tenth rib just referred to in connection with gastropnoxis. When the tenth rib is detached or floating its tip sticks out like that of the eleventh rib in this illustration. The same illustrations also demonstrate the anatomical fact that only a very small portion of the stomach is palpable through the soft part of the abdominal wall, when it is in normal position, because the larger part of it is concealed under the ribs and under the liver. So that the simple fact that we can see or feel a large part of the entire stomach projecting through the abdominal wall, when it is distended, is a sufficient evidence that the stomach is out of place. The stomach can be made visible through the abdominal wall by distending it artificially with carbon dioxide by means of an effervescent mixture containing tartaric acid and bicarbonate of soda.

The remaining organic diseases of the stomach necessitate all the intricacies of chemical and microscopical diagnosis for their detection. They include the various forms of acute and chronic gastric catarrh or, as they should preferably be called, the forms of acute and chronic gastritis, the various types of gastric or peptic ulcers, the various tumors of the stomach, especially cancer, which is becoming more and more frequent. Then there are numerous diseases of a general nature, such as tuberculosis, typhoid fever, glanders, lymphadenoma and syphilis, to be considered in the study and treatment of disorders of the stomach.

Whenever there is an organic disease of the stomach present it should be sought after with all the resources of modern clinical diagnosis. There should be no dallying with so-called stomach panaceas. Quite a number of the so-called incurable gastric diseases which have been allowed to go on to destruction of the glandular layer and absolute loss of peristalsis of the stomach are not incurable in themselves, but have become so from neglect, maltreatment, or procrastination. And even in those cases in which the practitioner is at present helpless, the rapid progress of medical art, especially as applicable to digestive diseases, promises a substantial gain in the near future.

**Bibliography.**—Hemmeter, 'Diseases of the Stomach,' in which there are 1,288 separate publications arranged categorically in separate chapters to which they refer especially, and over 1,000 references in the text; Ewald, 'Diseases of the Stomach,' translated into English by Morris Manges; Boas, 'Diagnostik und Therapie der Magenkrankheiten'; Riegel, 'Erkrankungen des Magens,' being Vol. XVI. of Nothnagel's 'Encyclopedia on special Pathology and Therapy'; Fleiner, 'Krankheiten der Verdauungsorgane'; Einhorn, 'Diseases of the Stomach'; Martin, 'Diseases of the Stomach'; Abercrombie, 'Investigations on Diseases of the Stomach'; Habershon, 'Diseases of the Abdomen'; Rosenheim, 'Pathologie u. Therapie des Verdauungs-

apparats'; Pick, 'Magenkrankheiten'; Brouardel et Gilbert, 'Traité de Médecine et de Thérapeutique,' Vol. IV.; Mathieu, 'Traité de Maladies de l'Estomac'; Hemmeter, 'Organic Diseases of the Stomach'; Leo, 'Krankheiten der Bauchorgane'; Robin, 'Traité de Thérapeutique appliquée,' fasc. XII. (article on indigestion by G. LeMoine). The modern literature of diseases of the stomach, intestine, liver, etc., up to 1904, is reviewed by John C. Hemmeter in 'Progressive Medicine,' December 1903, pp. 1-84.

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**Stom'ach-pump,** a small pump or syringe used for removing matter from the stomach, for washing it out, or for injecting fluids into it. It resembles the common small syringe, except that there are two apertures near the end, instead of one, which, by means of valves in them opening different ways, serve respectively as a sucking and a forcing passage. When the object is to extract something from the stomach, the pump is worked while its sucking orifice is in connection with an elastic tube passed into the stomach; and the extracted matter escapes by the forcing orifice. When it is desired to throw cleansing water or other liquid into the stomach, the connection of the apertures and the tubes is reversed. A pump may not be always procurable when the occasion for it arises, and a simple tube will in many cases answer the purpose as well, if not better. If the tube be introduced, and the body of the patient be so placed that the tube forms a downward channel from the stomach, all fluid matter will escape from the stomach by it, as water escapes from a funnel by its pipe; and if the outer end of the tube be immersed in liquid, there will be, during the discharge, a siphon action of some force. On changing the posture of the body, water may be poured in through the same tube to wash the stomach. For washing out the stomach a long flexible tube is also in common use, water being run in by means of a funnel attached to one end, and this end being afterward lowered so as to form the tube into a siphon.

**Stomata,** minute orifices or pores in the epidermis of leaves, etc., which open directly into the air cavities pervading the parenchyma. See LEAVES.

**Stomatitis.** See MOUTH, DISEASES OF THE.

**Stone, Amasa,** American business man and philanthropist: b. Charlton, Mass., 27 April 1818; d. Cleveland, Ohio, 11 May 1883. At 21 he engaged in the construction of railroad bridges and railroads, and soon attained high rank among constructors. In 1846 he entered into a partnership for the building of the Cleveland, Columbus & Cincinnati Railroad; in 1850 he was made president of that road and thenceforward resided in Cleveland. He was later engaged in the construction of the Cleveland & Erie Railroad; was managing director of the Lake Shore Railroad in 1872-4; and was president or director of several railroads and industrial corporations in Ohio. He gave largely to charitable institutions in Cleveland, and built and endowed an old ladies' home, and an industrial school. He also gave to Western Reserve University \$600,000, on condition that the university should be moved from Hudson to Cleve-



land, and that the classical department should be named in memory of his son, Adelbert College.

**Stone, Charles Pomeroy**, American soldier: b. Greenfield, Mass., 30 Sept. 1824; d. New York 24 Jan. 1887. He was graduated from West Point in 1845; served in the Mexican War and was brevetted captain; was chief of ordnance of the division of the Pacific; and subsequently settled in California. At the opening of the Civil War he became an officer of volunteers in the Union army, but after a short term of service was arrested, and was imprisoned in Fort Lafayette, New York harbor, February–August 1862. Upon his release he served in the Department of the Gulf, and was chief of staff to Gen. Banks, 1863–4. Later in the year he resigned from the army. He entered the service of the khedive of Egypt in 1870, rose from brigadier-general and chief of staff to be Ferik-Pasha, 1873–83, received numerous decorations and held confidential positions under the khedive. Returning to the United States he became the engineer in charge of building the foundation for the Statue of Liberty in New York harbor.

**Stone, Edward James**, English astronomer: b. London 1831; d. Oxford 1897. He was graduated from Queen's College, Cambridge, and in 1860 was appointed chief assistant at the Greenwich Observatory. In 1870 he was made royal astronomer at the Cape of Good Hope, in which position he prepared a catalogue of all stars to the 7th magnitude between the south pole and 25° S. declination. This he supplemented in 1891 by a catalogue of all stars to the 7th magnitude between 25° S. declination and the equator. In 1879 he was appointed Radcliffe observer at Oxford, holding the position till his death. Among his contributions to astronomical science were his deduction of the value of the solar parallax and his observation of the reversal of the Fraunhofer spectrum during an eclipse of the sun in 1874.

**Stone, Ellen Maria**, American missionary: b. Roxbury, Mass., 24 July 1846. She was a member of the staff of the 'Congregationalist' at Boston in 1867–8, in 1878 went to Samokov as a Congregational missionary, and was removed subsequently to Philippopolis, southern Bulgaria, and (1898) Salonica, Macedonia. In September 1901 she was kidnapped by brigands between Bansko and Djumia, Macedonia, and a ransom of \$110,000 for her and Mme. Tsilka, captured at the same time, was demanded. By subscription in the United States, \$65,000 was raised and the release of the prisoners followed. Her narrative appeared as 'Six Months Among Brigands' in 'McClure's' in May–October 1902, and in 1903 in book form.

**Stone, Frank**, English painter: b. Manchester 22 Aug. 1800; d. London 18 Nov. 1859. He originally painted in water colors, and in 1837 became a contributor to the exhibitions of the Royal Academy. Subsequently for more than 20 years he produced many works in genre and history, and on subjects of sentiment and imagination. Some of these are well known by engravings, particularly the companion pieces entitled 'The First Appeal' and 'The Last Appeal,' once very popular. He was elected an associate of the Royal Academy in 1851.

**Stone, James Samuel**, American Protestant Episcopal clergyman: b. England 27 April 1852. He was graduated from the Philadelphia Divinity School 1877, took orders, and was ordained and was rector of St. Philip's Church, Toronto, 1879–82, of St. Martin's Church, Montreal, 1882–6, of Grace Church, Philadelphia, 1886–95, and of St. James' Church, Chicago, since 1895. He has published 'Simple Sermons on Simple Subjects' (1879); 'The Heart of Merrie England' (1887); 'Readings in Church History' (1889); 'From Frankfort to Munich' (1894).

**Stone, Lucy Blackwell**, American reformer: b. West Brookfield, Mass., 13 Aug. 1818; d. Boston 18 Oct. 1893. She was graduated at Oberlin College in 1847 and in 1855 was married to Dr. Henry B. Blackwell, retaining, however, her own name. In 1869 she helped organize the American Woman's Suffrage Association; became connected with the 'Woman's Journal' in 1872, and was editor after 1888. Her lectures on woman suffrage made her known throughout the country.

**Stone, Marcus**, English painter: b. London 4 July 1840. He is a son of Frank Stone, A.R.A. He learned his art in his father's studio; exhibited his first picture in 1858 in the Academy, of which he became an associate in 1877, being elected an academicien in 1887. Among his better-known pictures are: 'Claudio Accuses Hero' (1861); 'On the Road from Waterloo to Paris' (1862); 'Stealing the Keys' (1866); 'Henry VIII. and Anne Boleyn' (1870); 'Sain et Sauf' (1875); 'Il y en a toujours un autre' (1882); 'A Gambler's Wife' (1885); and 'The First Love Letter' (1889).

**Stone, Marvin Cheater**, American inventor: b. Portage County, Ohio, 1842; d. Washington, D. C., 17 May 1899. He invented several small articles, and afterward discovered a method of imitating, in colored china, the famous "peach-blow" vase. He acquired a large fortune, and during his later years was engaged in many philanthropic undertakings.

**Stone, Melville Elijah**, American journalist: b. Hudson, Ill., 22 Aug. 1848. He began his journalistic career on the Chicago *Tribune*, but was not permanently settled in it until 1871, when he established the Chicago *Daily News*. In 1881, with Victor F. Lawson, he acquired the Chicago *Morning News*, changing its name to the *Record*. In 1888 he retired temporarily from newspaper work, and spent some years in Europe, and upon his return entered the banking business. In 1898 he became general manager of the Associated Press.

**Stone, Ormond**, American astronomer: b. Pekin, Ill., 11 Jan. 1847. He was graduated at the University of Chicago, and soon after was made assistant astronomer at the Naval Observatory at Washington. In 1882 he was appointed professor of astronomy and director of the observatory at the University of Virginia. He is the founder and editor of the 'Annals of Mathematics,' published by that institution, and a contributor to various scientific journals. He has made several important discoveries concerning nebulae and double stars.

**Stone, Thomas**, American patriot, signer of the Declaration of Independence: b. Pointon Manor, Charles County, Md., 1743; d. 5 Oct.

[Reprinted from *American Medicine*, Vol. VII, No. 14, pages 558-559,  
April 2, 1904.]

## THE USE AND ABUSE OF THE IMAGINATION IN THE EXPERIMENTS AND OBSERVATIONS IN MEDICINE.<sup>1</sup>

BY

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of Baltimore, Md.

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This Association was founded for the encouragement and diffusion of medical learning in the pathology of the digestion and metabolism. Its creed is very simple, requiring in the new member only will and devotion. It is our business to study the works of nature, and particularly of abnormal nature, as manifested in the human body, by observation and experiment, and it is our duty to conform our conduct to nature's laws. We believe that upon this line of investigation lies the true road of progress for scientific medicine. We do not wish individually to impose our ideas on others, but prefer to leave them to the operations of reason and judgment and in this sense we are free among ourselves.

If a brother go astray we let him alone, feeling sure that time will lead him back to the truth. Cicero tells us that time overthrows the opinions of men, and confirms the decisions of nature. With full confidence in this sentiment let us go on in our work? An effort should be made to arrange an occasional symposium on the same subject, that is, let the same subject-matter be discussed from the clinical as well as the surgical side, by reporters of that special meeting. Surgeons and clinicians do not meet often enough to discuss the borderland between medicine and surgery. Then those of a more scientific turn of mind, the lovers of physiology and pathology, should arrange with the clinical men to discuss subjects of mutual interest. For example, the diseases of metabolism, diabetes, obesity, uric acid diathesis, pancreatic and hepatic diseases can only be thoroughly ventilated in this way. Such discussion could be arranged between two reporters of a meeting, or by a motion a special subject could be agreed upon for general discussion. Considerable instruction should result from such conferences, for we have many clever thinkers in this Association, and latent convictions

<sup>1</sup> President's address, American Gastroenterologic Association, Washington, D. C., May 14, 1903.



have often only been brought out during a heated and interesting debate.

Great differences exist among medical men. We have general practitioners and medical men of research and experimental philosophers. This imposes upon us the necessity of enforcing a degree of selection in the choice of our new members. I cannot become reconciled to the thought that this union of knowledge and sentiment should ever be disbanded after so many years of fruitful and blessed activity. To you we leave the duty to perpetuate the union of scholarship and good fellowship. It is self-evident that we cannot accomplish our aim without criticism, but critical satisfaction has always been submerged beneath the positive elation over the splendid uprising of medical science at the beginning of the Twentieth Century.

There are many infatuations which exercise a kind of tyranny in medicine. To raise personal preferences to the dignity of a creed is not enough. A cult once established, a dogma once accepted—there can be no more freedom from analysis, no more independent criticism, no more permissible dissent. The usual procedure is to give unthinking assent. Mental indolence is, of course, at the bottom of this fashion. It is easier to accept an opinion than to form one. Never has the tendency to slavish partisanship been more general nor despotism of ready-made judgments more absolute than in these times of pretended scientific emancipation and so-called individualism.

It is dangerous to classify imperfectly-known data under general theories, and sound progress of science requires of us to be clear at every moment which elements in the system of science are hypothetic and which are the limits of that knowledge which is obtained by direct observation.<sup>1</sup> There are few students who possess that cold enthusiasm for truth which enables them to be always clearly conscious of the sharp line between attractive theory and observation acquired by hard and earnest work.

Speaking of the ebb of intellectual force, which we all from time to time experience, Mr. Bain<sup>2</sup> says: "The uncertainty where to look for the next opening of discovery brings the pain of conflict and the debility of indecision." These words have in them the true ring of personal experience. The action of the investigator is periodic. He grapples with a subject of inquiry, wrestles with it, overcomes it, exhausts both himself and it for the time being. He breathes a space, and then renews the struggle in another field. Now this period of halting between two investigations is not always one of pure repose. It is often a period of doubt and discomfort, of gloom

<sup>1</sup> Role of Hypotheses in Medical Research: W. Ostwald.

<sup>2</sup> Bain's Logic.

and ennui. "The uncertainty where to look for the next opening of discovery brings the pain of conflict, and the debility of indecision."

John Tyndall<sup>1</sup> states it is well worth the while of the scientific teacher to take some pains, and even great pains, to make those whom he addresses copartners of his thoughts. But it is by no means easy to clear his own mind in the first place of all haze and vagueness, and then to project into language which shall leave no mistake as to his meaning, and which shall leave even his errors naked, the definite ideas he has shaped. Much is possible to scientific exposition conducted in this way. Even before an audience like the present, it is possible to uncover to some extent the unseen things of nature, and thus to give not only to professed students, but to others with the necessary bias, industry, and capacity, an intelligent interest in the operations of science. Time and labor are necessary to this result, but science is the gainer from the public sympathy thus created.

It appears to be characteristic that every new view or statement in all domains of knowledge is announced with perfect self-assurance, in order to be impressive. And the inclination of human beings to dogma, and the deficient philosophic culture of large circles, has lent encouragement to this custom.

Yet little or nothing of the context of new things can in the strictest sense be proved by observation, and much less by experiment, which pretends to be a high judge of clinical medicine.

I do not desire to make you critically apprehensive by a paradox, but I cannot refrain from suggesting that really nothing can be proved by experience and experiment. Phenomena can be accurately observed, experiments can be precisely executed. One is enabled to arrange experience and experiment in a certain order, one can deduct one phenomenon from another. A certain, definite circle of knowledge may be established. One can even elevate one's views to a degree of certainty and completeness, and that is accomplishing much.

However, deductions in the minds of others are formed by everyone for himself. As far as one goes with his logic, one cannot prove anything by it. Everything concerning the opinions about things belongs to the individual—and we know very well that convictions do not depend upon insight but upon the will. Nobody grasps or understands anything except that which his will concedes. In knowledge, as well as action, the foreknowledge or prejudice decides everything—and prejudice, as its name indicates, is a judgment before investigation.

Philosophers may be right in affirming that we cannot

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<sup>1</sup> Scientific Use of the Imagination.

transcend experience; but we can at all events carry it a long way from its origin. We can also magnify, diminish, qualify and combine experience, so as to render it fit for purposes entirely new. We are gifted with the power of imagination, and by this power we can lighten the darkness which surrounds the world of the senses.

John Tyndall<sup>1</sup> says:

There are Tories even in science who regard imagination as a faculty to be feared and avoided rather than employed. They had observed its action in weak vessels, and were unduly impressed by its disasters. But they might with equal justice point to exploded boilers as an argument against the use of steam. Bounded and conditioned by cooperant reason, imagination becomes the mightiest instrument of the physical discoverer. Newton's passage from a falling apple to a falling moon was, at the outset, a leap of the imagination. When William Thompson tries to place the ultimate particles of matter between his compass points, and to apply to them a scale of millimeters, he is powerfully aided by this faculty. And in much that has been recently said about protoplasm and life, we have the outgoings of the imagination guided and controlled by the known analogies of science. In fact, without this power, our knowledge of nature would be a mere tabulation of coexistences and sequences. We should still believe in the succession of day and night, of summer and winter; but the soul of force would be dislodged from our universe; causal relations would disappear, and with them that science which is now binding the parts of nature to an organic whole.

All the facts which we have considered, the liability to error in whatever direction we may go, the infirmity of our minds in their reasoning power, the fallibility of witnesses and experimenters, lead the scientist to be specially sceptical with reference to any statement made to him or any so-called knowledge that may be brought to his attention. Professor H. A. Rowland made the following statement in an address made shortly before his death:

The facts and theories of physical science are so much more certain than those of history, of the testimony of ordinary people on which the facts of ordinary history or of legal evidence rest, or of the value of medicine to which we trust when we are ill—indeed, to the whole fabric of supposed truth by which an ordinary person guides his belief and the actions of his life, that it may seem ominous and strange that what I have said of the imperfections of the knowledge of physics is correct. How shall we regulate our minds with respect to it? There is only one way that I know of, and that is to avoid the discontinuity of the ordinary, indeed, the so-called cultivated legal mind. There is no such thing as absolute truth and absolute falsehood. The scientific mind should never recognize the perfect truth or the perfect falsehood of any supposed theory or observation. It should carefully weigh the chances of truth and error, and grade each in its proper position along the line joining absolute truth and absolute error.

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<sup>1</sup> Scientific Use of the Imagination.

If this latter injunction is followed out very little room is left for the use of the imagination in the solution of medical problems, and even when employed in a controlled and limited extent, its yieldings must always be submitted to the test of repeated demonstration, if possible by experiment. When imaginative power was left to develop questions of research unaided, it yielded only hypotheses, and these are the curse of medicine.

The ordinary crude mind has only two compartments, one for truth and one for error, indeed, the contents of the two compartments are sadly mixed in most cases; the ideal scientific mind, however, has an infinite number.<sup>1</sup> Each theory or law is in its proper compartment indicating the probability of its truth. As a new fact arrives, the scientist changes it from one compartment to another in order to keep it, if possible, in its proper relation to truth and error. Thus, the fluid nature of electricity was once in a compartment near the truth. Faraday's and Maxwell's researches have now caused us to move it to a compartment nearly up to that of absolute error.<sup>1</sup>

So the law of gravitation within planetary distances is far toward absolute truth, but may still need amending before it is advanced further in that direction.

The ideal scientific mind, therefore, must always be held in a state of balance which the slightest new evidence may change in one direction or another. It is in a constant state of scepticism, knowing full well that nothing is certain. It is, above all, an agnostic with respect to all facts and theories of science as well as to all other so-called beliefs and theories and cannot yield to temptations held out by processes of imagination. If the foremost American physicist thought it his duty to caution against the scientific absolutism of today in a domain to which the most precise and accurate methods are applicable, it is evident that the same caution is more directly applicable to researches in medicine, to which methods of equal accuracy are not applicable and in which more liberty is as a rule conceded to the power of imagination.

Care should be had lest this Association drift into that state which is commonly known as a "mutual admiration society." Fair-minded and conservative criticism is one of the most edifying and instructive forms of debate. Nine-tenths of all medical publications of the present day are simply compilations of scientific facts, to which no individual interpretation is added. Such compilations have in reality very little value unless the author is capable of associating with them conservative critical judgment, based on broad experience. Let us hope that the reports of the American Gastroenterologic Association will

<sup>1</sup> H. A. Rowland, *loc. cit.*



more and more become precise and accurate statements of critically digested and tested truths, in which nothing is stated simply on the authority of someone else, without having been again thoroughly considered and revolved in the brain of the reporter, and worked up by a systematic plan and order. At no point in the report to a representative scientific body should there be any doubt of the logical connection of the various parts of the report, and one argument should be logically succinct upon another. I have stated this because my personal experience has been that quite a number of reports have not given evidence of these qualities. They have been devoid of those evidences of mental digestion on the part of the writer, and of logical criticism which are the most unfailing proofs of broad experience, keen and conservative judgment, and a good and sane heart that always wishes and works for the best.



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SOME PHYSIOLOGIC ASPECTS OF EHRLICH'S SIDE-  
CHAIN THEORY, AND ITS APPLICATION TO THE  
PHYSIOLOGY OF DIGESTION

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*Reprinted from International Clinics, Vol. II., Fifteenth Series*

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## SOME PHYSIOLOGIC ASPECTS OF EHRLICH'S SIDE-CHAIN THEORY, AND ITS APPLICATION TO THE PHYSIOLOGY OF DIGESTION<sup>1</sup>

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IN the so-called side-chain theory of immunity by Ehrlich, we find the most ambitious introduction of chemical conceptions. Long before Ehrlich, Pasteur introduced the notion of molecular asymmetry into chemical science and called attention to the importance of the conception of configuration in dealing with certain chemical problems.

In 1894, during an investigation of far-reaching importance on the bodies of the sugar group, Emil Fischer made some remarkable statements on the behavior of certain enzymes in the fermentation of sugars. He pointed out that in order to work as ferments, the enzymes must possess a certain stereo-chemical structure bearing a certain definite relation to the stereo-chemical structure of the sugar. Without this relation fermentation cannot take place. In order to make his meaning plain, Emil Fischer employed a figure which has since become famous. In speaking of certain glucosides, he said, "Enzyme and glucoside must fit into each other as a key into a lock in order that the one may be able to exert a chemical action on the other." Furthermore, Fischer suggested that the idea of related molecular configuration of enzyme and fermentable body may prove of value in physiologic investigation as well as in chemistry.

Apparently we have in this prediction of Fischer, made 11 years ago, the basis of Ehrlich's hypothesis, and the often quoted symbolic analogy used by Ehrlich: "*Wie ein Schlüssel in das Schloss*" is an expression borrowed from Emil Fischer.

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<sup>1</sup> Received for publication, January 28, 1905.

The opinion that the antibodies are themselves enzymes is erroneous, because the antibodies do not act upon the invading toxins (ferments, bacteria) according to the type of a ferment. These invading substances (toxins, etc.) are not split up or oxidized; no hydrolysis takes place as occurs under ferment action; furthermore, the antibodies are consumed or used up, which does not occur with enzymes. Enzymes do not appear in the endproduct of the catalysis, but the antibodies unite directly and combine with the toxin. Antibody does not act upon toxin like pepsin upon albumin, but like an acid upon a base.<sup>1</sup>

This conception, if true, brings the solution of problems of the chemical nature of antibodies within the range of probability, for if it could be definitely proved that they are enzymes they would, like all enzymes, escape the stoichiometric analysis of the chemist; at least, up to the present time there is no way of ascertaining the exact chemic composition of enzymes.

Ehrlich attributes antitoxin production to the cells that are especially sensitive to any poison; for example, in cases of tetanus toxin the antitoxin he supposes is produced by the nerve-cells. Gruber and Vaillon oppose this view. The ease with which a group of cells can be poisoned must not be confounded with avidity for that particular poison. Grassberger and Schattenfroh, Gruber, and others have shown that under a definite poison certain organs whilst showing a sufficiently great avidity to the poison are not irreparably or only slightly damaged, and other organs (on the other hand) possessing only a very slight avidity for the same poison suffer severely. Avidity is here identical with chemic affinity.

Toxin, according to Ehrlich, is a kind of spoiled, disintegrated protoplasm (cytoplasm or bacterioplasm, as the case may be). If we assume this we can understand how cells may be very sensitive to a toxin and yet not have an avidity for it; they cannot catch or take it up. For example, nerve-cells are highly sensitive to the catabolic products or results of broken-down protoplasm, but physiology forbids us to assume that nerve-cells are actively concerned in assimilating and taking up such catabolic products (*Abbauprodukte* of Gruber).

This toxin assimilation and transformation may be a property

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<sup>1</sup> Jacoby, *Ergebnisse der Physiologie*, 1. Jahrg., I. Abtheil., S. 244.

of such cells and organs (closely related genetically to the intestinal tissue) that have had much skill in neutralizing and metamorphosing abnormal substances (gland cells). According to Ehrlich, the antitoxins are important constituents of the architecture of protoplasm; many facts support this view; for example, the injection of antitoxin causes no formation of antibodies.

We should not be surprised if the higher differentiated cells (nerve-cells) should have a great avidity for toxins. On the other hand, the production of antitoxin may be a function of a lower order of cells (gland cells). We must distinguish between sensitiveness to toxin poison (*Vergiftbarkeit*) and avidity (chemic affinity) for poison. Ehrlich attributes the production of antitoxin (tetanus) to cells that are most sensitive to this toxin (nerve-cells) (nerve-cell damage objectively is the one most readily noticeable by the observer). Now hens are extremely sensitive to direct cerebral applications of tetanus toxin, but on intravenous injection of this poison in large quantities they form large quantities of antitoxin *without being damaged in their nervous system*. If the production of antibodies was a rôle of the "sensitive" cells pre-eminently and exclusively, this would be a puzzle.

We must in this difficulty distinguish between (1) chemical detrimental influences on highly differentiated cells that are readily poisoned (very sensitive), but produce no antitoxin, and (2) detrimental influences on cells not so sensitive (not easily poisoned), but producing the antitoxins.

Ehrlich's theory that the antitoxin is formed by the cells most sensitive to the poison is somewhat difficult to comprehend, because it ascribes a very laborious task, complicated chemic work, to cells most readily poisoned, that is, injured, and not to cells comparatively freer from the poisoning influence.

The most widely accepted view is that saturated toxin and antitoxin combinations (neutral mixtures) are indifferent for the normal organism—only the full, unbound toxin (dissociated toxin) of the mixture, can have an effect in causing the production of antibodies. Grassberger and Schattenfroh give the experimental evidence that immunization of animals can be accomplished at one operation, that is, active immunization, with the production of demonstrable antitoxin in the blood, by neutral and overneutral mix-



tures.<sup>2</sup> In other words, toxin-antitoxin mixtures that were saturated with antitoxins were *not* indifferent for the animal body. Here we must attribute the immunization to the toxin-antitoxin combination. There are two possibilities here, (1) the ability to cause the production of antitoxin must be assigned to the toxin-antitoxin combination *as such*, by virtue of its content of implicated or combined toxin, or (2) we must accept an extensive dissociation of the substances implicated in the mixture, when the latter reaches the organism, each of the dissociated groups entering into effect, that is, the freed toxin leading to the production of antitoxin in the organs capable of producing it, whilst at the same time the freed antitoxin protects the cells sensitive to the toxin. It is conceivable that the complex toxin-antitoxin molecule still has affinities for the organs that are capable of producing antitoxin, whilst the avidity of the toxin-sensitive cells is reduced or lost.

The greatest difficulties are met in attempting to explain the active immunization of oxen and heifers by supersaturated serum mixtures (Ueberserum Gemische), that is, mixtures the toxic affinities of which have been completely saturated in glass vessels and that liberate no dissociable toxin on being heated.

The consumption of antitoxin by the (vergiftbare) cells having a great avidity therefore may keep step with the production of antitoxin by the cells capable of producing it, and in that case then it would not be possible to demonstrate much antitoxin in the blood.

In an address on the relations between chemical constitution, distribution, and pharmacologic action, Ehrlich has emphasized the great significance of the peculiarities in chemic constitution of elements foreign to the organism, that is, as far as their distribution in the various cells and their differing effects are concerned.

Löw had defended the view that these foreign elements, for instance, narcotics, antipyretics, pigments, actually enter into real syntheses with the living protoplasm; in other words, that they conduct themselves like the assimilable food substances. This view is energetically refuted by Ehrlich,<sup>3</sup> for two reasons: (1) These foreign substances are very easily extracted from animal tissues,

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<sup>2</sup> Beziehung v. Toxin u. Antitoxin, Grassberger u. Schattenfroh, Hygien Instit., Univ. Wien, February, 1904.

<sup>3</sup> Von Leyden, Festschrift, I. Bd., also *Gesam. Arbeiten zur Immunitätsforschung*, p. 607.

and (2) he had never observed pigment changes, that is, staining reactions occur on injection of suitable basic dyes or stains into the *living organism*, although these color changes occur so readily *outside* of the living body when the amido groups are replaced by aldehyde radical. If the coloring substances actually entered the protoplasm molecule in a substituting manner, such permanent changes by pigments exerted in the living body ought to have been occasionally observed in the exceedingly large number of experiments hitherto made. But the substances capable of assimilation, which represent the specific nutritive substances of protoplasm, enter into a very firm combination with protoplasm, from which they can only be split off by very energetic means,—boiling with acids, for example.

The injection of ordinary food-stuffs, for instance, the various albuminous and proteid substances, causes in the organism the production of very specific antibodies (coagulines, precipitines). Upon this fact Ehrlich assumes that in the process of the assimilation of food substances a similar combination of the food molecule with the receptors of the protoplasmic molecule takes place, as occurs during the combination with toxins.

But whilst the toxin is relatively simple in structure (compared with the food substance) and the toxic effect of its toxophore group can be readily transferred to the molecule of protoplasm by its receptor, the albuminous or proteid nutritive substances, however, are very complex in chemic structure, which must be more and more disintegrated before they can be made useful to the protoplasm.

According to the symbolism of Ehrlich, this is best accomplished when the receptor that anchors the albumin molecule to the protoplasm has at the same time an enzyme-like group which attends to the further molecular disintegration of the giant molecule of albumin.

The receptor for the toxins has only one single haptophore group which unites with the haptophore group of the toxin, but the receptor for the nutritive albumin molecule has two groups, first a haptophore group which anchors down the albumin molecule, and, second, a zymophore group which effects the fermentative disintegration of the albumin molecule. Those of the first kind, namely, which act as receptors for toxins, Ehrlich designates as "*Receptors of the first order*" (Rezeptoren I Ordnung). Those of the second

kind he designates "receptors of the second order" (Rezeptoren II Ordnung). Still more complicated are his Rezeptoren III Ordnung,

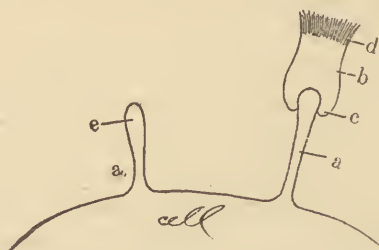


FIG. 1.—Receptor of first order. *e*, haptophor complex; *b*, attracted toxin molecule, with haptophor, *c*, and toxophor group, *d*.

which effect the anchoring down of complex bodies resulting from disintegration of bacteria and animal cells,—bodies which after their

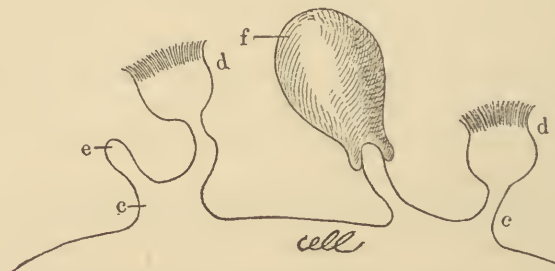


FIG. 2.—Receptor of second order. *e*, haptophor group; *d*, zymophor group; *f*, a molecule of nutritive substance that has been attracted.

liberation circulate in the blood as "Hemolysins," "Bacteriolysins," and "Cytolysins."

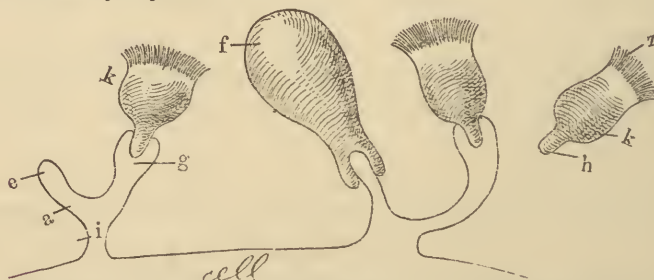


FIG. 3.—Receptor of third order. *e*, haptophor group; *g*, complementophile group; *k*, complement with, *h*, haptophor group, and, *z*, zymotoxic group; *f*, molecule of nutritive substance that has been attracted.

In the action of these lysins two substances must work together,—the "immune body" (which, by the way, has seven different des-



ignations by different investigators) and the complement. The "immune body" liberated into circulating blood corresponds to the receptor when it is attached to the protoplasm molecule. The immune body (amboceptor) must be built up like the receptor, that is, the immune body must contain a haptophor group which attends to the anchoring down of complex disintegration products of bacteria—red blood-corpuscles, etc., and a second group, which, however, does not by itself act as an enzyme, as it does in the "receptors of the II order," but is conceived as only having the ability to attract to itself ferment-like bodies circulating in the blood, the so-called "*complements*." Only after this has occurred can the anchored-down substance undergo further disintegration and utilization.

The functions of these three different kinds of receptors is conceived as occurring in different manners. For, whilst the super-regenerated and liberated receptors of the first order destroy the effect of the toxins by simple and direct combination with them, the receptors of the second order, that is, the coagulins, agglutinins, and precipitins, after their combination with the nutritive albuminous substances, can produce coagulation, precipitates, and agglutinations immediately and directly by means of the zymophor group that belongs to them. The receptors of the third order, however, are ineffective, although liberated into the blood, even after their connection with the cells that were utilized for their production. They are ineffective until the complements, which are present normally in the blood, have united with the receptors belonging to the cell and exerted their ferment-like action.

These different receptors bring about the anchoring down of the ordinary food substances as well as of the toxins and the disintegrated products of bacteria and cell. As long as the receptors are in the living protoplasm molecule of the cell and are uncombined, their action is to attract these substances, useful as well as harmful. But as soon as they are liberated into the blood by super-regeneration, they detract from the protoplasm molecules of the cell, because they already unite in the blood with the substances named, and thus they protect the cells from their effects. In case of toxins and disintegrated parts of bacteria and cells, these effects would be deleterious and harmful; in case of nutritive albuminous substances, these effects would be beneficial.



It was in his extension of his "side-chain" theory to the normal physiologic cell nutrition that Ehrlich met with difficulties. For he could not exclude that receptors in excess were formed and liberated into the blood. Now if receptors circulating freely in the blood are conceived as protecting the cell from toxins and products of disintegrated metabolism by uniting with these deleterious substances in the blood, we must admit the same possibility as occurring between freely circulating receptors and the food substances, which, however, in this case, when receptors unite with food substances in the blood, do not protect the cell, but rob it of its nutrition. The liberated receptors, when circulating in the blood, Ehrlich designates as "haptins." To the haptins of the first order belong the antitoxins and the ferments; to the haptins of the second order belong the agglutins, coagulins, and precipitins; to the haptins of the third order belong the cytolytins, hemolysins, and bacteriolysins. It was these haptins of the third order, when generated in excess and circulating freely in the blood, that gave the difficulty in explaining the application of the side-chain theory to physiologic cell nutrition. Nutrition of the cell is impossible if the haptins already unite with the nutritive substances in the circulating blood, and prevent the nutritive substances from reaching the cells. Ludwig Aschoff has attempted to explain away this difficulty by asserting that a great part of these haptins were removed from the body through the secretions, that another part was consumed in the disintegration of the nutritive substances in the blood, and that the introduced food substances are present in such great amounts that there is always an excess present for the nutrition of the cell. To these explanations of Aschoff we might reply that it is not quite intelligible why the haptins of the first and second order, those that neutralize toxins in the blood, and disintegrated products of bacteria and cellular protoplasm, should not also be removed from the body in the secretions, when there is need for them caused by the presence of substances with which they could combine in the blood. The second explanation of Aschoff that the food substances are present in such excessive amounts that there is always an excess left over for the nutrition of the cell, may also, if applied to the haptins of the first order, be conceived as working a damage to the cell, for if the haptins of the first order are not

present in sufficient quantity the toxin molecules will combine with the protoplasm molecules of the cell, and cause its destruction.

From this it is evident that the application of the side-chain theory to processes of normal cell nutrition and assimilation, although interesting and feasible, is not yet practical nor based on objective experimental evidence. But as Ehrlich has shown, inasmuch as the substances gained artificially by means of immunization are nothing else but the tools of normal cell life which have been separated by the immunizing process from the locality of formation and isolated, it is probable that the physiologic processes of secretion and assimilation can be profitably studied from the stand-point of Ehrlich's theory. Furthermore, it is conceivable that conditions like malnutrition, without demonstrable organic disease, and some of the forms of obesity or hypernutrition, could be profitably studied from the same stand-point.

#### THE ACTION OF DIGESTIVE FERMENTS VIEWED FROM THE STAND-POINT OF EHRLICH'S SIDE-CHAIN THEORY

From the discovery of Delezenne we know that fresh extract of pancreatic gland can exert no digestive action on proteid by itself alone.<sup>4</sup> But if a small amount of succus entericus is added to pancreatic extract, tryptic digestion at once begins. The succus entericus contains enterokinase (Pawlow and Chepowalnikoff). Enterokinase can very easily be gained by permitting fibrin to remain a certain time suspended in succus entericus. It then becomes attached to the fibrin. If the fibrin thus charged with enterokinase is brought together with pancreatic juice at 0°, no tryptic effect occurs, but it does occur when the mixture is brought into the incubator. These observations suggest that the enterokinase, which in itself is ineffective, acts as an amboceptor, chaining the trypsin to the fibrin. Delezenne showed that the enterokinase of the dog could act as an amboceptor for the trypsin of animals of different species. Enterokinase, it is true, is not so resistant to heat as the amboceptors of hemolysis.

Bayliss and Starling consider that the secretion of pancreatic juice is not reflex, as was originally held by Popielski and Wertheimer, but that it is due to an exciting substance which is pro-

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<sup>4</sup> *Compt. rend. de la Soc. de Biol., Paris, Dec. 28, 1901, p. 1161.*

duced in the intestinal mucous membrane under the influence of the acid gastric juice. If the mucosa of the jejunum and duodenum is exposed to the action of a 0.4 per cent. HCl, a body is produced which when injected into the blood-stream in minimal doses produces a copious secretion of pancreatic juice. This substance they term *secretin*, and it is associated with another substance which lowers arterial blood-pressure. This secretin is, of course, not identical with enterokinase, for secretin is an inorganic substance, not an enzyme, and it is not specific to different kinds of animals, but is the same substance in all animals. Secretin is not destroyed by boiling. Whilst it sets up the secretion of pancreatic juice by way of the circulation, it does not activate pancreatic juice for proteids like enterokinase does. The accelerating action which enterokinase is claimed to exert upon trypsin digestion, according to Pawlow, has received another interpretation by the discovery of Otto Cohnheim.<sup>5</sup> Hofmeister, Salvioli, and Neumeister had observed the disappearance of peptones when they came in contact with intestinal mucosa, and they interpreted this as a restitution of the peptones into native albumin by some power inherent in the mucosa. This is denied by Cohnheim, who has discovered a new enzyme formed in the intestinal mucosa, which he terms *erepsin*, and which has no effect on fibrin and ordinary proteids, but acts only on peptones and a part of the albumoses, converting them into simpler compounds; and S. Ssalaskin discovered that this erepsin is a normal constituent of the succus entericus.<sup>6</sup> Concerning the relative functions of enterokinase (of Pawlow) and erepsin, no clear conceptions can as yet be formulated. According to the view of some physiologists, these two substances may be identical. According to others the enterokinase acts simply as an amboceptor for the trypsin. According to Ehrlich's theory, this enterokinase ferment, in order to do the work that it is known to be able to accomplish, would have to have a very complicated structure, that is, one haptophore group for the albuminous body, a second haptophore group for the trypsin, and, thirdly, an additional zymophore group, which, however, does not go into effect until after the trypsin has been anchored down. These conceptions started from the experiments and suggestions of Fischer, which I have represented at the

<sup>5</sup> Hoppe-Seyler's Zeitschr. f. physiolog. Chemie, Bd. 33, Hft. 5 and 6, S. 451.

<sup>6</sup> Russki, Archiv. path. klin. Medic. i. Bacteriol., Bd. xiv, p. 3, Sept., 1902.



beginning of this report,<sup>7</sup> and were later on extended and applied to all fermentative processes in the light of Ehrlich's theory, namely, that simple ferments, like the chymosin or rennet, are supplied with a specific haptophor and with a more generally active toxophor or zymophor group. This conception is analogous to that of toxins. The enterokinase he conceives as amboceptor.<sup>8</sup> Just as the action of toxic alkaloids differs from that of bacterial poisons only by the nature of their combination with the thing to be acted upon, so also with the ferments. If the zymophor group is once tied down to the fermentable substratum, it acts simply as a catalyzing substance, like dilute acids. The specific fermentative force would be then attached to the haptophor group, and the force that acts catalytically upon the most widely different bodies would be tied down to the zymophor group of the ferments. These applications of the Fischer and Ehrlich conceptions (narrated at the beginning of this article) are made by Oppenheimer, and were no doubt inspired by an article by G. Bredig.<sup>9</sup> The main points in the conception are the action of two different groups in organic ferments, and their specificity. But there are many difficulties standing in the way of a general application of the Fischer-Ehrlich hypothesis to the action of all ferments. It requires a tremendous effort of the imagination to conceive that the very simple fermentable bodies like amygdalin and cane-sugar should have specific haptophor groups for the yeast ferment, and although antibodies have been experimentally produced against chymozin (rennet), all efforts to find anti-diastases and anti-pepsin, etc., have been without result. Martin Jacobi<sup>10</sup> also cautions against the identification of toxin action with fermentative processes. Ferments are substances the actions and effects of which are to a great extent comparable to the catalyzers of inorganic chemistry.<sup>11</sup> They influence chemical transformations without taking part in the reaction or ap-

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<sup>7</sup> Oppenheimer. Zur Theorie der Fermentprocessor. Münch. med. Wochschr., 1901, No. 16, p. 624.

<sup>8</sup> See Oppenheimer.

<sup>9</sup> Die Elemente der chemischen Kinetik, mit besonderer Berücksichtigung der Katalyse und der Fermentwirkung, Ergebnisse der Physiologie, Jahrgang 1.

<sup>10</sup> Ergebnisse der Physiologie, Jahrgang 1.

<sup>11</sup> See Ueber Katalyse, by Wilhelm Ostwald, Leipzig, 1902; and Die chemische Organization der Zelle, by Hofmeister.



pearing in the end products. Toxins, on the other hand, are substances which are chemically combined within the organism. Toxins and antitoxins are much more resistant to various deleterious influences than the real ferments. In opposition to these facts, Oppenheimer<sup>12</sup> emphasizes that the action of ferments is not only catalytic, but he conceives that they are also changed during their action, and he even asserts that combinations of ferments occur with other bodies; for instance, that the enterokinase can be bound to the fibrin. To this I have to oppose that actual transformation of enzymes, whilst they are performing their characteristic reaction, has been by no means satisfactorily demonstrated. All that we know definitely in this connection is that the action of the organic enzymes is arrested by their own products, and by the presence of salts in excess of a certain percentage in the solution. This inhibition of enzyme action does not mean transformation of the enzyme; and, secondly, the fact that enterokinase can become attached to fibrin by no means proves that a chemical combination between the two exists. It may be simple mechanical attachment.

As long as there is no satisfactory explanation of the nature of enzyme action, nor even an accurate chemical analysis of a single enzyme, the application of the Ehrlich side-chain theory to the physiology of digestion is merely ingenious speculation. The conception which has the greatest probability in its favor is that the organic enzymes are catalyzers in a colloidal state. This is the view held by Professor Bredig. Newer investigations concerning the laws that control enzyme action have given no evidence that there are any principal differences in the nature of the actions between the organic enzymes and the catalyzers of inorganic chemistry.

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<sup>12</sup> Loc. cit.





# History of the Clinical Recognition of Gastric Ulcer.

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ADDRESS BEFORE THE AMERICAN GASTRO-  
ENTEROLOGIC ASSOCIATION, ATLANTIC CITY,  
JUNE, 1904. : : : : : :

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Baltimore.

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*Reprinted from The Journal of the American Medical  
Association, January 7, 1905.*

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CHICAGO:

PRESS OF AMERICAN MEDICAL ASSOCIATION  
ONE HUNDRED AND THREE DEARBORN AVENUE.  
1905.





## HISTORY OF THE CLINICAL RECOGNITION OF GASTRIC ULCER.

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Succinct histories of the development of clinical conceptions on special diseases are very rare. This is partially explicable by the scarcity of historical data concerning early clinical thinking and by the confusion that has been brought into the accounts of the classical writers of medicine by the facts that the identical disease is designated with different names by different authors, and also that the exact diagnosis was rarely verified by operation or autopsy.

In the following sketch of the history of the clinical recognition of gastric ulcer, conclusions were based only on such cases as were substantiated in the manner just mentioned. In the writing of Hippocrates we find no statement which would justify us in concluding that the "Father of Medicine" was familiar with ulcer of the stomach as we conceive it to-day.

It is stated (Lebert) that Hippocrates treated Pericles for intense abdominal pain (gastralgia) by hellebore and flaxseed poultices.<sup>1</sup> I shall return to the Hippocratic literature on this subject in the latter part of this article.

A careful review of a German translation of Galen reveals no knowledge of peptic ulcer, though undoubtedly both Hippocrates and Galen give accounts of vomiting of blood in the sequence of digestive disturbances and abdominal pain.

It is impossible to personally scrutinize the writings of the historical clinicians for any statement that might

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1. I have seen this statement quoted also by Talmage in an address to medical graduates, but have not been able to trace the source nor authority for same.—J. C. H.

be interpreted as a distinct clinical recognition of gastric ulcer. According to Lebert,<sup>2</sup> from whom also Welch<sup>3</sup> has derived most of his information concerning the history of clinical recognition of peptic ulcer, it is not until the sixteenth century that a clinical record available for our purpose can be found. It occurs in the writings of Johann Bauhin, the elder brother of Caspar Bauhin (1550-1624), and may be found in "Boneti Sepulchretum." It refers to a physician's wife, 18 years old, who suddenly showed symptoms of a perforation into the peritoneum, and died four days afterwards. In her abdomen was discovered besides gas, fluids and food remnants, a perforation in the middle of the stomach near the fundus; there were black contents in the stomach and clotted blood had been evacuated by the bowels.

From the second half of the sixteenth century dates another observation by Marcellus Donatus, which refers to a man 59 years old, who, after continued vomiting and pains in the stomach, was found at the postmortem examination to have near the pylorus at the lower end of the stomach an ulcer—*tunicam interiorem exesam*—a very graphic descriptive expression.

Courtial describes an oval opening in the anterior part of the stomach, with callous edges in a young woman who had suffered from gastric symptoms since her youth.

Littre found in the case of a man who had suffered from various affections of the stomach, and finally from hemorrhages, a round ulcer near the pylorus.

One of the first ulcers leading to a fistula in the stomach which is recorded in the literature so far known, seems to be associated with a case of Duverney. Similar observations were described in the first half of the previous century by van Swieten, Klein, Wenker, Iodac, Atkinson, Petit, Eckmuller, Cireaud, Helm, and Kade. It is not, however, quite certain to what the trouble in the various cases might rightly have been attributed, whether to the presence of a simple ulcer, or to a circumscribed abscess of the stomach region or a combination of both. The probabilities are, however, that the observation of van Swieten and Wenker were genuine cases of peptic ulcer.

Records of cases of healed ulcer of the stomach we

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2. Krankhelten d. Magens, Tübingen, 1877, p. 180.

3. Pepper's System of American Medicine, vol. II.

already possess for the sixteenth and seventeenth centuries, by Forestus and Schenk von Grafenberg (1531 to 1598). In this connection should be mentioned an observation from the close of the preceding century by Reil, in which the scar of a healed gastric ulcer had become adherent to the mesenteric glands. The radiant formation of such a scar at the lesser curvature of the stomach has been aptly described according to a specimen in Meckel's collection. Older observations concerning abnormal conditions of the form of the stomach, with median contraction, by Blase, Mangold, Heister, Sandifort, Sömmering, Morgagni, etc., allude in a measure to such ulcers. In a number of cases symptoms of chronic stomach trouble existed beforehand, and frequently mention is made of callous bands, which would point to scars of earlier existing ulcers. In the last century mention is often made of adhesions of the stomach to adjacent parts (Mead, Murray, Santessen, Westring, etc.) of rupture of the stomach (principally through an ulcer), of death from excessive hemorrhage, also mainly attributable to a chronic peptic ulcer.

A good brief description, with excellent illustrations, was given at the close of the eighteenth century (in 1793) by Matthew Baillie. To Matthew Baillie unquestionably belongs the credit of having first accurately described, in 1793, the anatomic peculiarities of simple gastric ulcer.<sup>4</sup> At a later date he published three good engravings of this disease.<sup>5</sup> Baillie's concise and admirable description of the morbid anatomy of gastric ulcer was accompanied by clinical data, and seems to have had little or no influence in directing increased attention to this disease.

By far the best description of this disease up to the date of its publication is by Voigtel, at the beginning of the eighteenth century. The following description is quoted from Lember:<sup>1</sup> "Frequently ulcers are found in the membranes of the stomach. Oftener they progress from the interior to the exterior; they are merely superficial cancers or perforations. They have in common a peculiar appearance. Frequently they are surrounded by an inflammatory thickening and hardness, and then again it is not pos-

4. *The Morbid Anatomy of the Most Important Parts of the Human Body*, London, 1893, p. 87.

5. *A Series of Engravings, accompanied with explanations, etc.*, London, 1799.



sible to detect near or around them any distinctive abnormal formation of the stomach. They appear as if "a piece of the stomach had been cut out with a knife," and the edges so healed as to make a smooth boundary all around the opening; at times the gastric tissue about the opening has condensed." The subsequent remarks point likewise to an admirable knowledge with the whole evolution of the disease on the part of Voigtel and his contemporaries, Meikel, Reil, etc. The words used by Voigtel in describing the appearance of this gastric lesion, namely: "As if a piece of the stomach had been cut out with a knife."—remind one of the expression of Rokitansky<sup>6</sup> used much later, and which is much oftener quoted, namely: "As if a piece of the stomach had been cut out with a punch."

Many observations, accompanied by diverse commentaries, are found in the early scientific literature concerning spontaneous perforations of the stomach, the greater part of which may rightly be classed here.

Toward the end of the eighteenth century we encounter Hunter's theory of the origin of gastric perforations, attributing them to the erosion by the gastric juice; although based on the authority of Spallanzani, this hypothesis lost ground very rapidly, notwithstanding the support given it by a number of important authorities. Carswell managed to bring it again into transitory favor. In the year 1800 Joseph Morin stated that perforation of the stomach was a result of a protracted local inflammation of the gastric membranes. He likewise speaks of stagnation in the blood vessels, with a change in the direction of the flow of the blood and autodigestion, as some of the causes. According to the very pretty historic compilation of Lefevre, Lerons and Chaussier, in the year 1808, presented to the Paris Medical Association reports of their observations of perforated gastric ulcers accompanied by adhesions of the spleen.

Very interesting history also is found in the defense of a person by Chaussier against the charge of poisoning, in 1818, when the latter proved that a perforation of the stomach had taken place after previous prolonged ulceration. Similar cases have come up frequently since that time. Cruveilhier relates that there was a move-

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6. Lehrbuch d. Pathol. Anatomie.

ment on foot to attribute the death of one of his cases of chronic gastric ulcer to poisoning, when he proved that the true cause of the perforation in question had been a previously existing ulcer in the stomach. The dissertation of 1819 by Lainé offers for those times very sound opinions about this perforation, and describes the deleterious action of the digestive fluid as succeeding ulceration. He also emphasizes the importance of studying the antecedents of a case. The expression "perforation by erosion" from now on appears more frequently. Lainé also recommends, for forensic reasons, not only chemical inquiry, but also an examination of those parts of the anatomy through which the alleged poison is supposed to have passed into the stomach.

Rausch, in his classification of gastric ruptures, designates those incident to a real ulcer, often with callous edges, as one of the main groups. Similar results are reached by Ebermaier, who, in addition to his own, cites cases by Henkel, Mole, Baron, Gérard, Desgranges, Trinius, Besker, Spitta, and Thomissen. To all these cases he attributes a chronic, many times unknown course, frequently with easily discernible symptoms, especially cardiac symptoms. The frequency with which the rupture takes place near the pylorus is pointed out by him, but he seems to be unable to determine the cause of this phenomenon. Cancer and ordinary inflammation, however, are not regarded as having causal significance.

In 1824, Abercrombie published a brief, but for his time a very remarkable description of this disease. Some of his observations clearly refer to the *ulcus simplex*; indeed one of the cases reported to him by Wood refers to a perforated ulcer of the duodenum. His confusion of cases of gastric cancer and other malignant growths with those of simple ulcer, shows how undefined his views were.

We now have become acquainted with two phases of the history of chronic ulcer—the first being one of the isolated observations beginning with the tenth century, the second beginning with the close of the eighteenth and with the early part of the nineteenth century, and occupying itself with the establishing of a collection of those isolated observations as done by Voigtel, but emphasizing more of the pathologic anatomic point of

view; on the clinical side, too, much attention is paid to the perforation itself.

Cruveilhier has the distinction of being the first to subject this disease both clinically as well as anatomically to a thorough and intelligent pathologic examination. The tenth issue of his great "Pathological Anatomy," from the beginning of the third decade of the nineteenth century, 1829-1835, gives evidence of an extensive personal experience on the subject.

Cruveilhier<sup>6 1-2</sup> in the first volume of his work on Pathologic Anatomy, published between the years 1829 and 1835, for the first time clearly distinguished ulcer of the stomach from cancer of the stomach and from ordinary gastritis. He gave an authoritative and full description of gastric ulcer from the anatomic, the clinical and the therapeutic points of view.

Among his observations are those concerning the Greek professor, Gall, from the end of the year 1828 and beginning of the next; one from December, 1829, about a charcoal burner, who died soon after the perforation of his stomach; one from the beginning of the year 1830, concerning the famous chemist, Darcet; one from the same year concerning a gastric ulcer which had cicatrized—and with respect to this case we learn from his twentieth issue that the person in question died in 1834 from a perforated stomach. Not only are the anatomic aspects—i. e., rapidly developing, chronic ulcer, closing up, scarring over, perforation, hemorrhage from the coronary artery of the stomach, from the splenic artery, malformation of the stomach, contraction of the pylorus through the agency of scarring—well described, but also a good foundation is laid for clinical and therapeutic work.

We thus emerge into the modern phase, in which a correct and broad interpretation of anatomic and clinical facts of the influence of hygiene, diet and therapeutics takes place, and thus order and understanding are introduced into this chaos of observations.

In Germany we are indebted to Rokitsansky for a classical treatise on the peptic ulcer, based on a large clinical and pathological experience, well analyzed. This excellent work became rapidly known.

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<sup>6 1/2</sup>. Anatomie pathologique du Corps humain, vol. I, Paris, 1829-35, No. 10 and No. 20; and vol. II, Paris, 1835-42, No. 30 and No. 31.

Next to Cruveilhier, Rokitansky has had the greatest influence on the modern conception of gastric ulcer. In 1839 this pathologist gave a description of the disease based on an analysis of 79 cases.<sup>7</sup> The anatomic part of his description has served as a model for all subsequent writers on this subject everywhere. A few years later von Jaksch extended the pathologic knowledge of the gastric ulcer (to be sure, more from his clinical experience than from a strict analysis of bedside records), by a series of thorough clinical investigations.

From 1830 to 1840 observations and compilations appear frequently in the medical literature of almost all countries. According to Lebert,<sup>1</sup> rich collections for causal interpretation are found in the *Bulletins de la Société anatomique de Paris*, also in *Archives générales de Médecine*, in the "Annual Reports" of the last 20 years of Canstatt,<sup>8</sup> the Proceedings of the London Pathological Society, etc. Among the older journal articles and dissertations that have appeared is the Thesis of Duval in the year 1852 (Paris), one of the earliest of the better French compilations. Lebert<sup>1</sup> also refers to the publications of one of his pupils, Bissegger, as containing his own views often expressed in the Zürich clinic, and also an analysis of its rich material, together with clinical histories.

After Virchow, in 1855, developed his views on the hemorrhage-necrotic origin of the simple peptic ulcer, a series of good dissertations appeared under his editorial supervision, among which especial mention should be made of those by Steiner, 1868, and Wollman, 1868. Among the English authors, Crisp, Ashborne, Chambers, Habershon, Handfield-Jones, etc., but especially Brinton, have done excellent work. From the latter emanated the largest compilation, with excellent anatomical and clinical data. Habershon has also made valuable clinical additions to our knowledge of this disease.

From the beginning of scientific inquiry cited in the preceding, to the year 1868, there is, as we have seen, a vast accumulation of clinical data, but out of all of this literature, according to Lebert, not 100 are of genuine objective merit.

7. Oesterlich Med. Jahrb., 1839, vol. xviii (abstract in Schmidt's Jahrb., vol. xxv, p. 40).

8. Canstatt's Jahresberichte.



Cruveilhier's work of 1856, made known in the *Archives Generales de Medicine*, contains for those times and for the present no new matter beyond what was presented in his previous publications, but impresses us with the great anatomic and clinical experience of this wonderful pathologist.

Trousseau, in his *Clinique Medicale*, gives a review of the essentials, which acts in a stimulating manner on medical thinkers, but is, of course, incomplete, which is to be expected of clinical lectures, however important they otherwise may be.

Bamberger's description is an excellent sketch of the subject. The work of Ziemssen (in his Encyclopedia, Ziemssen's *Handbuch d. spec. Path. u. Therap.*), on the treatment of chronic gastric ulcer, represents the best knowledge of the Munich clinic.

As early as 1845 Schiff shows that hemorrhagic localized infiltrations of the mucous membrane of the stomach result from an irritation of certain parts of the brain. After a number of other experiments, he published the results of his investigations in his "*Leçon sur la digestion.*" In 1852 Lebert became acquainted for the first time with the hemorrhagic type of the growth of chronic gastric ulcer. In 1855 Virchow made known his views on this matter, and brought into general favor the acceptance of a hemorrhagic necrotic origin of the peptic ulcer. Müller has the distinction of having proved, in 1859, that the ligation of the portal vein results in numerous hemorrhagic erosions of the stomach, particularly in the pyloric region. Pavy later on showed the same thing in the case of larger ulcers through ligation of branches of the gastric artery. For the best and most exhaustive experiments on the circumscribed hemorrhagic infiltrates in the mucous membrane of the stomach, we are indebted to Ebslein.

Since the ushering in by Cruveilhier and Rokitsansky of the modern era in the history of the gastric ulcer, the era of exact objective investigation, medical literature abounds in articles on this disease. But it can not be said that the importance of these works is at all commensurate with their number or that they have added very materially to the classical descriptions given by Cruveilhier and by Rokitsansky. Perhaps most worthy of mention of the works of this later era are the article by Jaksch relating to symptomatology

and diagnosis, and of Virchow relating to etiology, the statistical analyses by Brinton, and the contribution to the treatment of the disease by Ziemssen and by Leube.<sup>9</sup> In 1860, Ludwig Müller<sup>10</sup> published an extensive monograph on gastric ulcer. The most modern literature on the subject is contained in the works of Riegel.<sup>11</sup> Prof. Wm. H. Welch<sup>12</sup> gives a short résumé of the history of the clinical recognition and pathology of gastric ulcer, taken largely from Lebert. In the new *Handbuch der Geschichte der Medicin*, by Neuberger and Pagel,<sup>13</sup> the history of gastric ulcer is rather neglectfully treated. It seems that the author, George Korn, had no knowledge of the interesting studies of Abercrombie, Voigtel, Littré, Matthew Baillie, Cruveilhier and the other clinical and pathologic workers mentioned in the preceding. The article is interesting for the histology and pathology of digestion, the history of the stomach tube, etc., but for the history of the development of clinical ideas on any single gastric disease, little help can be obtained from this otherwise very interesting article. On page 693 of this article, Korn asserts that Hippocrates already described some of the symptoms of gastric ulcer as a special disease which was called "*sphacelous disease*," or "*morbus niger*," because black masses in the form of clumps were either vomited or passed by the bowels. I have looked up this passage in Hippocrates<sup>14</sup> and, while there is great temptation to credit the "Father of Medical Literature" with the first trustworthy knowledge of gastric ulcer, I regret to report that his account is not even approximately correct for this disease, but would cover that also of gastric carcinoma and even of secondary gastric hemorrhage, due to cirrhosis of the liver. Some

9. Jaksch: *Prager Vierteljahrschr.*, vol. III, 1844; Virchow: *Arch. f. path. Anat.*, vol. v, p. 362, 1853; and A. Beer: "Aus dem. path. anatom., Course des Prof. R. Virchow in Berlin, Das einfache duodenische (corrosive) Magengeschwür," *Wiener med. Woch.*, Nos. 26, 27, 1857; Brinton: *On the Pathology, Symptoms and Treatment of Ulcer of the Stomach*, London, 1857; V. Ziemssen: *Volkmann's Samml. klin. Vorträge*, No. 15, 1871; Leube: *Ziemssen's Handb. d. spec. Path. u. Therap.*, vol. VII, Leipzig, 1878.

10. *Das corrosive Geschwür im Magen und Darmkanal*, Erlangen, 1860.

11. *Erkrankungen des Magens*. In the fourth volume of Penzoldt u. Stintzing's *Handbuch d. speciellen Therapie*, p. 316, also pp. 437 and 438 are contained 150 bibliographical and historical references on gastric ulcer.

12. *American System of Medicine* (edited by Pepper), vol. II, p. 480.

13. Vol. II, p. 666.

14. Sydenham Society edition.

have thought the dietetic treatment which Hippocrates recommended for his *morbus niger* gave evidence that he recognized it to be the disease we know as gastric or peptic ulcer. But even this hope is destroyed by a critical investigation of the diet of Hippocrates for this purpose. In 1899 Rudolph Bandel, on the incentive of Prof. R. Fleischer, of Erlangen, investigated the writings of Hippocrates for his knowledge on dietetics. It is published in a small pamphlet entitled "*Ansichten u. Ausprüche des Hippokrates über die Ernährung vom Gesunden und Kranken, etc.*" (Inaugural dissertation, Erlangen.) In this publication we find nothing to confirm the supposition that the diet of Hippocrates gave evidence of his knowledge of gastric ulcer. The term which Hippocrates gives to the vomited masses in *morbus niger* is *atra bilis* (black bile), which expression maintained itself in medical literature until 1740, when F. R. Hoffmann demonstrated that the seat of *morbus niger* is the stomach. His words are as follows: "Simultaneously with the destruction of the substance of the stomach, the vessels are corroded or broken open, and these open vessels furnish the blood which is expelled by vomiting. We have to assume that the vessels are corroded by sour and acid juices, when a sharp gastric pain precedes the vomiting, and when the vomited bloody masses are black and acid at the same time, make the teeth stand on edge, and irritate the mouth and gullet."

Morgagni (1682-1771), a contemporary of the prominent Italian anatomists, a pupil of Valsalva and Albertini, and a friend of Lancisi, in his book on "The Seat and the Causation of Diseases," does not agree with the view of F. R. Hoffmann just expressed, but holds that patients who die of *morbus niger* were suffering from a kind of gangrene of the stomach; that they did not die of loss of blood, but of a kind of poisoning of the blood, which infected the brain. It is interesting to note here that Morgagni described in this work the condition known as "continuous gastric secretion" (gastric succorhea) occurring in a German nobleman in Bologna, who died later with symptoms of gastric tetany.

The designation *ulcus ventriculi* was first used by the versatile Jena clinician, Johann Peter Frank (1745 to 1821.) It is regrettable that the writings of this scholarly asclepiad are being gradually forgotten, for the mod-

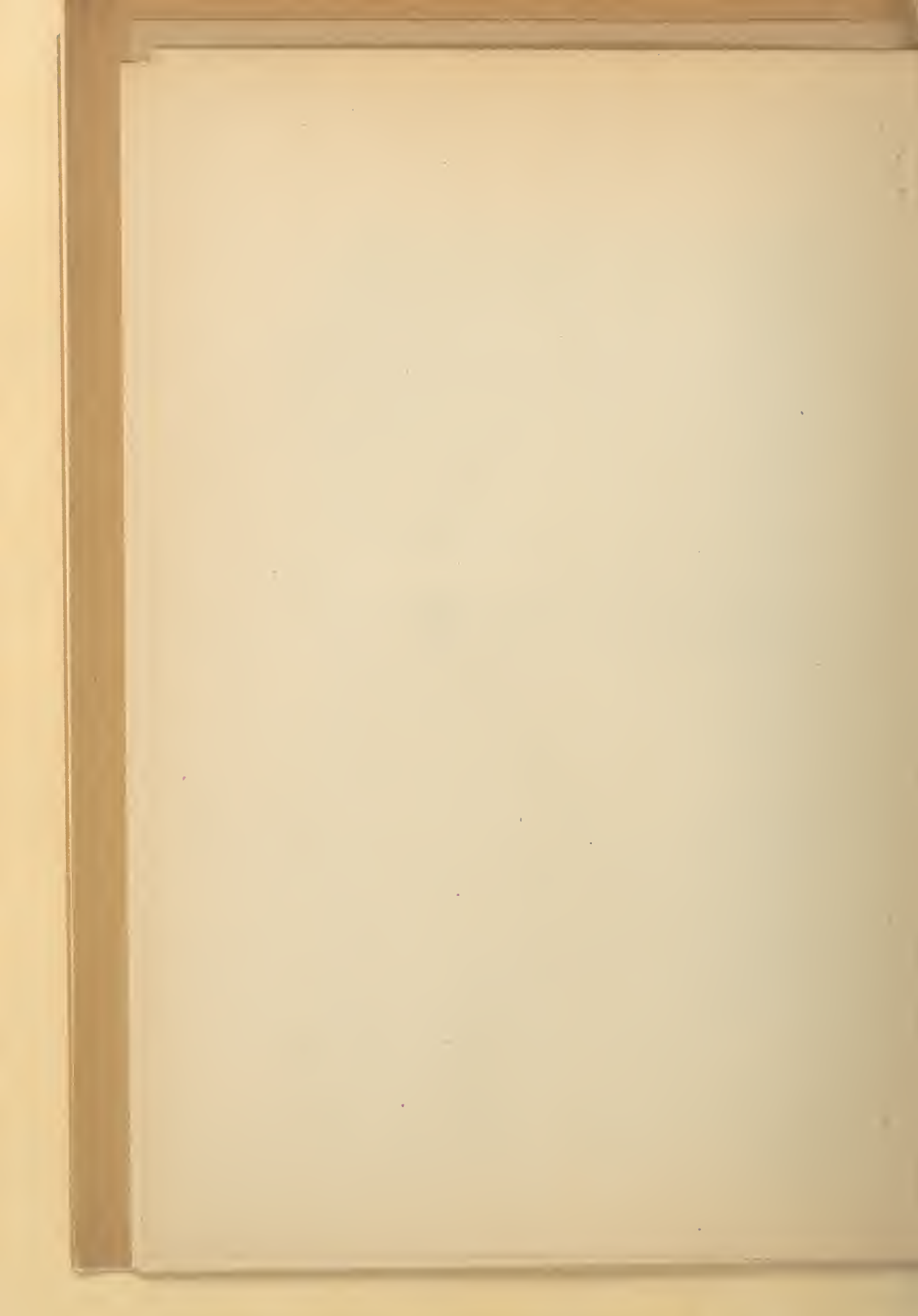
ern treatment of gastric ulcer dates from him. The insistence on absolute rest in bed, the application of snow, or crushed ice to the stomach, the great regard for dieting (milk and bouillon in small portions), all show exceptional clinical experience. The best that is known on gastric ulcer and gastric diseases in general up to 1850 is presented in the work of William Brinton. Since the descriptions of Cruveilhier, Rokitansky and Virchow, the pathologic conception and the clinical conception of the gastric ulcer have received no notable advance. The further students of this disease, Trousseau, Kussmaul, Ziemssen, Leube, C. A. Ewald, von Mering, Fleiner, Boas, Rosenheim, Riegel, Penzoldt, furnished clinical elaborations, purely.

It might be mentioned before concluding, that the first surgical intervention for gastric ulcer was undertaken in 1881 by Rydygier. For further history of gastric surgery, see Hemmeter.<sup>15</sup>

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15. Diseases of the Stomach, third edition, p. 348. For history and literature of gastric ulcer, see same work, pp. 486-526, containing 248 literary references on the subject.









## MUSIC AT THE UNIVERSITY OF MARYLAND.

By JOHN C. HEMMETER, M. D., Ph. D., etc., Professor of Physiology and Clinical Medicine, University of Maryland, Baltimore.

At no time in the history of the University of Maryland has there been a special department for the teaching of music as a part of educational discipline. From time to time, however, the students organized musical clubs, under the names of Glee Club, Mandolin or Banjo Club, which, however, had only an ephemeral existence. No fixed organization nor any experienced master of the art of music to teach the musical students. In 1903, however, the writer organized "THE UNIVERSITY OF MARYLAND MUSICAL ASSOCIATION," which in October of that year had sixty active singers, an orchestra of eighteen instruments, and a mandolin and banjo club. The vitality of this society, as manifested by the talent and industry of its members, and the able instruction of Professor Theodore Hemberger, was evident in a public concert which was given at Lehmann's Hall in the Spring of 1904, in which the chorus produced some of the most difficult classical choral compositions. The manner in which these choruses were sung met with the highest commendations from the ablest musical critics of the city of Baltimore. Dr. B. Merrill Hopkinson, recognized as the finest baritone soloist in the city, and an alumnus of our University, sang the solo in Grieg's "Landsighting," together with the Musical Association.

This association has a very promising future before it, as it is under the direction of one of the ablest masters of music in Baltimore.

Music is everywhere regarded in civilized countries as an exponent of general culture. As a general rule, it can be said that the student who devotes one evening a week to a musical association is a man of refinement, and aspires to higher culture. The success of the Musical Association of the University of Maryland depends entirely upon the students themselves. If

they will not attend the rehearsals regularly, nor feel it their duty to contribute to the reputation of their alma mater by enhancing the cultivation of an art which has purely esthetic objects in view, then the society cannot exist. And if it fails to succeed, the students have no one but themselves to blame. The beginning years of every organization are the most difficult in its existence. There is every prospect as the society gets older that it will become more self-supporting, and may by its concerts be able to contribute not only to the academic functions and entertainments, but also by public concerts to contribute to the general endowment fund. All those who have once become members, therefore, *should unswervingly and loyally adhere to the Musical Association during their entire course at the University.* For those who have voices and are musical it should be a pleasure and a duty to belong to an organization which contributes so much to refinement and esthetic improvement.

Unfortunately, there are quite a number of students who, although they have good voices and are musical, do not join the association simply because they do not believe they can advance in their medical examination by the culture of music. Well, if a man could sing or play himself through anatomy, physiology and pathology, the Musical Association would soon have the entire student body on its waiting list. But music, really, can help the student through his examination by refreshing his mind, in directing other brain centres into activity, whilst those transiently exhausted through study will thereby become rested.

"The man who hath no music in his soul,  
Nor is moved by concord of sweet sounds,  
Is fit for treason, stratagem and spoils."

—SHAKESPEARE.





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[Reprinted from *American Medicine*, Vol. IX, No. 10, pages 398-401,  
March 11, 1905.]

## ADVANCES IN THE PHYSIOLOGY AND PATHOLOGY OF THE PANCREAS, AND THEIR APPLICATION TO THE DIAGNOSIS OF PANCREATIC DISEASES.\*

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Exact physiologic knowledge concerning the functions of the pancreas dates from the year 1848, when Claude Bernard discovered that the secretion of this organ was capable of digesting fats, but he missed its tryptic action entirely. In 1857 Corvisart ascertained that the same secretion had the power of digesting proteid material. And although Frerichs in 1849, and Bidder and Schmidt in 1852 published comprehensive monographs on the total digestive process, nothing of medical interest was brought forward concerning the physiology and pathology of the pancreas until Friedrich<sup>1</sup> published his memorable communication on this subject in 1875.

From 1875 to 1887 was another period of fruitless endeavor. Then came the work of Müller<sup>2</sup> and the epoch-making discoveries of von Mering and Minkowski in 1889, who demonstrated in a manner exempt from all criticism that diabetes could be experimentally produced in the dog by extirpating the pancreas, and that the appearance of sugar in the animal's urine was accompanied by all the emblems of glycosuria as it occurs in the human being. It must be admitted that De Dominicas<sup>3</sup> was about the same time experimenting in the same manner, and had arrived at the same results, but he did not publish them until 1892.

Speaking of the ebb of intellectual force, which we all from time to time experience, Alex. Bain says: "The uncertainty where to look for the next opening of discovery brings the pain of conflict and the debility of indecision." These words have in them the true ring of personal experience. The action of the investigator is

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\* Address delivered by invitation of the Medical Society of Greater New York, February 8, 1904.

periodic. He grapples with a subject of inquiry, wrestles with it, overcomes it, exhausts, it may be, both himself and it for the time being. He breathes a space, and then renews the struggle in another field. Now this period of halting between two investigations is not always one of pure repose. It is often a period of doubt and discomfort, of gloom and ennui. "The uncertainty where to look for the next opening of discovery brings the pain of conflict and the debility of indecision." This describes approximately the state of mind we are in at present regarding the applications of physiology to the diagnosis of pancreatic disease.

On the basis of numerous investigations into the pathologic histology of the pancreas in cases of diabetes, it was established that many cases of this type of disease are due to atrophy, fatty degeneration and tumors of the pancreas. Particularly have the degenerations of the islands of Langerhans been associated with diabetes. But it must be explicitly emphasized that in some cases of very severe diabetes no changes whatever were demonstrable in the pancreas in spite of very careful macroscopic and microscopic examination. Richard M. Pearce has recently furnished more confirmatory evidence that the islands of Langerhans, though originating through a proliferation and differentiation of the cells of the primitive secreting tubules of the pancreas, eventually become wholly independent structures anatomically. Pearce's studies in development of these interstitial islets were made on the human embryo. On the basis of physiology, histology, pathology and embryology, therefore, the pancreas as it now appears represents an organ within an organ. The glandular parenchyma is concerned with an external secretion, "the digestive pancreatic juice"; the islands of Langerhans are identified with an internal, if not secretion, certainly control of carbohydrate metabolism.

There are three requisites which conservative clinicians must demand of all published assertions concerning the clinical pathology of the pancreas: 1. A concrete and precise account of the objective and subjective signs and symptoms. 2. Quantitative and qualitative chemic analyses of feces, blood and urine after the ingestion of weighed amounts of proteid carbohydrates and fats; preferably each given alone. 3. Accurate description of the findings that are discoverable either at operation or at autopsy.

In very few of the more important contributions to

this subject are these three requisites fulfilled with that regard for detail which the importance of pancreatic disease requires. Even in the very valuable paper by Müller,<sup>4</sup> which in other respects is a scholarly contribution, the supposed anatomic changes in the pancreas, upon which he at times bases important conclusions, are not always confirmed either by autopsy or operation.

Future experimental aims will have to test (1) the possibility of separating the islands of Langerhans, concerned in control of carbohydrate metabolism, from the part of the pancreas concerned in secretion of the digestive juice; (2) the demonstration that active proteolysis may take place in the intestinal canal in the entire absence of pancreatic secretion.

In our efforts to study the effect of the pancreas upon the various food substances, we are considerably embarrassed by the possible effects that the succus entericus may have upon the same articles of diet. Hundreds of thousands of crypts of Lieberkühn are pouring their secretion into the intestinal lumen, and comparatively little has until recently been known about this secretion, except that it is capable of inverting the disaccharids. Pawlow was the first to show that one of the main actions of succus entericus was to reinforce and intensify the action of pancreatic juice, particularly its proteolytic power. Fresh pancreatic juice has practically no proteolytic power, but if fresh pancreatic and intestinal juice are mixed together, the result is a powerful proteolytic mixture, though neither juice by itself has any proteolytic activity. The substance contained in intestinal juice which has this action upon pancreatic juice, has been named by Pawlow "*enterokinase*" (he speaks of it as a ferment of the ferments). It mainly reinforces tryptic activity, but also has a similar but slighter activating influence on the fat-splitting ferment of the pancreas.

The influence of bacteria on intestinal proteolysis was first investigated by Busch<sup>5</sup> at the surgical clinic of the University of Bonn. The person upon whom the investigations were made had been gored by a mad steer in such a way that a fistula had been formed, opening into the upper part of the jejunum, so that the entire gastric chyme, together with the bile, pancreatic juice, and the secretion of Brunner's glands, escaped exteriorly, and none of these substances could enter the lower section of the small intestine. Although large quantities of food substances were taken by the mouth, this patient seemed doomed to death from inanition, because the food



materials after they had undergone gastric digestion and become mixed with the pancreatic juice and bile, escaped exteriorly before any further digestion or absorption could take place. Busch then resorted to feeding the patient by stuffing liquid and semisolid food into the lower section of the opened intestinal canal. Curiously enough, he succeeded in restoring the strength and weight of the patient, and in maintaining him in the nitrogen equilibrium. This rapid recuperation by nourishment being introduced into the lower opening of the fistula proves that digestion can be carried on in the intestinal canal in the entire absence of gastric or pancreatic juice, bile, or the secretion of Brunner's glands. The digestive process could have been effected either by the succus entericus, which, according to Demant<sup>6</sup> possesses no proteolytic properties, or by microorganisms. Busch seemed inclined to attribute to the succus entericus the power of dissolving coagulated egg albumen, but in none of his experiments can the action of the proteolytic microorganisms be eliminated. Concerning the action of succus entericus on protein substances, former views held that it is without influence on boiled white of egg and meat, but according to Thiry<sup>7</sup> it has the power of dissolving fibrin. It cannot transform albumoses into peptone (Wenz<sup>8</sup>). I have gone over critically the literature given in this latter article, and also that in Hammarsten<sup>9</sup> of those investigators who attribute a proteolytic action to the succus entericus. But in none of them can the action of bacteria be eliminated. This is particularly true of the experiments of Schiff,<sup>10</sup> and those of Gachet and Pachin.<sup>11</sup> When the succus entericus was collected from animals and sterilized by filtration through a Pasteur filter and saturated with crystals of thymol, and the experiments were conducted under aseptic precautions, the succus entericus exhibited no proteolytic action. I was formerly disposed to attribute any proteolytic action recorded in the experiments of Busch to the action of proteolytic microorganisms. Busch inclosed coagulated egg albumen in small gauze sacs, and determined both the wet and the dry weight of the precipitated albumen used in his experiments. Attaching a string to the sacs, he permitted them to descend into the lower opening of the fistula. After they had remained in the intestine for about five hours, he withdrew them by means of the string, and determined the weight of the dry residue of albumen that had remained, and found that a loss of weight had

taken place, varying from 5% to 35% of the introduced substance. Brücke<sup>12</sup> also favors the view that this proteolytic digestion is due to the intestinal bacteria.

In 1900, however, I showed that extracts from fecal matter, when thoroughly sterilized and proved to be sterile by test culture, still showed a remarkable proteolytic and amylolytic power, which was due to the presence of unorganized enzymes,<sup>13</sup> and later on Otto Cohnheim<sup>36</sup> discovered in this succus entericus a ferment which while it has no action on native proteids, like fibrin and egg albumen, still has a very powerful action on proteoses and peptone, which it rapidly and completely breaks up into simple substances like ammonia, leucin, tyrosin, and the hexone bases. Cohnheim has named this ferment "erepsin." Hamburger found that erepsin is also present in human intestinal juice, and it is not identical with enterokinase nor zymolysin (zymolysin is the name which Starling has given to enterokinase). The products of erepsin action are not discoverable in the blood or lymph stream. Hamburger therefore supposed that they were resynthesized into proteids during the process of absorption. Embden and Knoop<sup>37</sup> however found neither a regeneration into coagulable (native?) albumin nor a further splitting up to occur from peptone, in the intestinal mucosa.

These recent contributions show that we have been in error in supposing that digestion in the entire absence of gastric and pancreatic juice was exclusively due to bacteria. It may be partly due to bacteria, but when a certain stage in the digestive process has been reached, erepsin (which is a very powerful enzyme) no doubt accomplishes the rest of the proteolytic work. It is also possible, from my results, that the succus entericus contains a proteolytic ferment very closely allied to trypsin, if not identical with it, in those cases in which the pancreatic secretion is prevented from being poured into the intestine; for I found subsequent to the experiments published in *Pflüger's Archiv*. l. c., that when the duct of Wirsung was ligated or stenosed, that a ferment could be extracted from the feces which could convert fibrin into peptones in an alkaline medium (accordingly it could not have been pepsin). This ferment was also found in the feces of a human patient in whom the pancreatic duct was stenosed by a huge pancreatic cyst.

All of these results go to show the difficulty in the way of facilitating the diagnosis of pancreatic diseases by judging from defective proteolysis as observed on

undigested proteids in the fecal matter. Proteolytic ferments may be secreted in the succus entericus when those of the pancreas cannot enter the intestine, and again even when the pancreatic juice freely enters the intestine, it may not become active for proteids because of some inflammatory or degenerative process in the duodenal and ileal mucosa which prevents the formation of enterokinase or zymolysin. Thus this prospective aid to diagnosis is beset with many difficulties, for impaired proteolysis as observed on the feces may be due to many different deviations from the normal.

*The Anatomy and Physiology of the Pancreas.*—A recent and at the same time most valuable contribution to this subject is by Dr. Eugene L. Opie.<sup>14</sup> I will pass over the description of the embryology and development of the pancreas, as not of absorbing interest to the clinician. In his description of the two ducts, the larger one, the duct of Wirsung, which enters the intestine in company with the common bile duct, and the smaller or accessory duct, that of Santorini, which terminates in the papilla situated nearer the stomach than that of the larger duct—he emphasizes that the duodenal orifice of the accessory duct is very minute, and joins the duct of Wirsung, into which doubtless pours its contents in the great majority of individuals. Opie has dissected the ducts after injection in 100 subjects. The two ducts were present in every instance, but one or the other was occasionally so small that it was found with difficulty. In 10 of the 100 instances the two ducts failed to anastomose within the gland, and in four additional subjects the two ducts were united by such a minute branch that they might be regarded as independent of one another. In 20 instances the duodenal end of the duct of Santorini was not patent. Thus these figures demonstrate that in at least two-thirds of all individuals the duct of Santorini cannot act as an accessory outlet, when the duct of Wirsung is occluded. In a considerable number of specimens the orifice of the duct of Santorini, though patent, was so minute that its functional significance was slight, and in 11 of the 100 specimens the duct of Santorini, on the contrary, was equal in size or larger than the duct of Wirsung, so that during life it was doubtless the outlet for the larger part of the pancreatic juice. The two ducts unite to form the short common channel, the diverticulum of Vater, which is subject to almost as much variation as the pancreatic ducts themselves. In 11 instances of the 100 subjects examined by Opie, no diver-

ticulum was present, and the two ducts entered the duodenum separately at the summit of the bile papilla. The duodenal orifice of the diverticulum of Vater had an average diameter of 2.5 mm., and the length of the diverticulum varied from 1 mm. to 11 mm., and only in 30 of the 100 specimens did the length equal or exceed 5 mm. These dimensions are significant because they show that a calculus which has become impacted within the orifice, will completely fill the diverticulum and occlude both ducts.

Physiologists and pathologists are now more and more appreciating two functionally diverse elements of the pancreas. First, cells which supply the intestine with important digestive ferments, those which are concerned in the manufacture of pancreatic juice, and second, cells having no communication with the ducts of the gland, but in intimate relation with the bloodvessels, and producing an internal secretion concerned in carbohydrate metabolism. Cases have from time to time been reported in which it was claimed the entire pancreas had been destroyed by disease, and yet the carbohydrate metabolism did not appear disturbed. We can understand how the stomach and intestines may step in and take up the digestive functions of the pancreas vicariously, but this is not intelligible so far as the internal secretion is concerned. In such cases in which the pancreas is apparently destroyed, the maintenance of normal carbohydrate metabolism might be explained by the discovery of Helly, who found lobules of pancreatic parenchyma situated within the papilla of the duct of Santorini, and also immediately below the duodenal mucosa. Occasionally these misplaced portions of pancreatic tissue were provided with an independent duct, and constituted a true accessory pancreas. In 1,800 autopsies performed at the Johns Hopkins Hospital, small masses of aberrant pancreatic tissue were found by Opie imbedded in the wall of the stomach or of the intestine in 10 cases at a variable distance from the pancreas. In two instances two accessory glands occurred in the same individual. These accessory and aberrant pancreatic glands may, in exceptional cases, explain the maintenance of the normal carbohydrate metabolism in those exceptional cases in which the pancreas was reported apparently entirely destroyed.

Proceeding to a consideration of the histology of the pancreas, Opie graphically describes the ferment-secreting cells, which are large and contain zymogen granules,



presenting characteristic variations during different stages of secretion, and forming the secreting acini. Scattered among the secreting acini, and several times the size of a single acinus, are the round oval bodies composed of polygonal cells grouped together to form short tortuous columns which unite with one another in such a way that space is left for a network of wide capillary bloodvessels. These interacinar islands are surrounded by capillary vessels which, when injected, appear, tortuous dilated and resemble the glomeruli of the kidneys. These islands of Langerhans consist of columns of cells in intimate relation with a rich vascular supply, and having no communication with the pancreatic ducts. They are ductless glands resembling the adrenal and parathyroid bodies. They are not concerned in the elaboration of the pancreatic ferment, and abundant evidence has shown that the islands of Langerhans exert an influence upon the carbohydrate metabolism through an internal secretion. Opie refers to the pancreas of a child who died of diabetes. The disease in this case was hereditary, and affected six members of the same family. The number of the islands of Langerhans was only a third of that usually and normally present. It suggests the possibility that diabetes will occasionally be the result of a congenital anatomic defect in the pancreas.

*Development and Pathology of the Islands of Langerhans of the Pancreas.*—Before the American Association of Pathologists and Bacteriologists, at the meeting held May 12, 1903, Dr. R. M. Pearce reported an exhaustive study of these groups of cells in a large collection of anatomic material, including 21 human embryos of different stages. The paper had essentially an embryologic and histologic bearing, but emphasis was laid upon the fact that the cells of the islands of Langerhans gave evidence of a remarkable resistance to degenerative processes. This makes it conceivable that we may eventually succeed in destroying the digestive or ferment producing cells of the pancreas in a living animal, leaving the islands of Langerhans intact. It has occurred to me that possibly this might be produced by the pancreatic juice itself, or by inducing an autolysis of the digestive cells of the pancreas through the influence of its own digestive ferment after the trypsin has been activated by enterokinase. In an autopsy in a case of diabetes mellitus, in which the patient had recovered from the symptoms of glycosuria, but had eventually succumbed to conse-

quences of cholelithiasis, I observed a partial autolysis of the glandular apparatus of the pancreas, whereas the islands of Langerhans did not appear diseased. Dr. R. M. Pearce, in a private conversation with me, was of the opinion that congenital syphilis might so affect the pancreas that the glandular cells would degenerate and the islands of Langerhans remain comparatively intact.

It seems to me that the functional exclusion of one or other of the two acting cell groups of the pancreas is the only exact way of arriving at conclusions concerning the role of the islands of Langerhans in carbohydrate metabolism, and it does not appear impossible that they may be isolated physiologically in one of the ways suggested.

*Acute and Chronic Pancreatitis.*—Before proceeding to the most recent contributions on the subject, I will have to refer to two American publications, one by W. S. Thayer<sup>15</sup> and one by Eugene Opie.<sup>16</sup> Thayer's conclusions were as follow: 1. Acute pancreatitis must be suspected in cases in which glycosuria develops with or following chronic cholelithiasis. 2. In cases of glycosuria with liver cirrhosis. 3. Cases of glycosuria with hemochromatosis. 4. Cases of glycosuria developing after attacks of supposed pancreatic colic. Pancreatic calculi can only be diagnosed by discovering them in the stool. Pancreatic cysts can be recognized from their position, but primary pancreatic cancer is often latent. Cancer of the pancreas should be suspected in cases of obstructive icterus with enlarged gallbladder, rapidly developing cachexia, and no, or only very slight, enlargement of the liver. Opie, in his contribution on "Chronic Interstitial Pancreatitis," made the following clinical conclusions: 1. It is more frequent in men than in women. 2. The most frequent cause of chronic pancreatitis is obstruction of the ducts of Wirsung from any cause. 3. Ascending infection of the pancreatic duct may cause this condition when the duct is not obstructed. 4. General or localized tuberculosis may cause profuse pancreatitis. 5. This disease is frequently brought about by the same causes which produce cirrhosis of the liver. As a rule, the chronic process attacks at first the interlobular tissues, later on, the acini themselves, and last of all, the islands of Langerhans. Only in very advanced cases does diabetes occur. 7. The pancreas is frequently the seat of a chronic inflammation in cases of Lænnec's cirrhosis of the liver, which is then characterized by diffuse proliferation of the interacinar tissue.

A similar pathologic condition accompanies also the hyaline degeneration of the islands of Langerhans, and the process known as hemochromatosis.

*Chronic Indurative Pancreatitis.*—S. M. Melkich<sup>17</sup> reports two highly instructive cases of chronic pancreatitis. The true nature of the malady, however, was ascertained at the laparotomy. In a female of 38, the principal symptoms were those of bile retention. In another, a woman of 22, among many other symptoms the most poignant was violent attacks of colic with considerable elevation of temperature. This writer, in agreement with a former publication by myself<sup>18</sup> and a very instructive paper by Reginald H. Fitz, to be reported, asserts that the diagnosis of chronic pancreatitis presents immense difficulties, and is as a rule not recognized before autopsy. According to Melkich this disease is either caused by alterations in the bloodvessels on the basis of alcoholism, syphilis or arterial sclerosis, or secondly by bacterial and catarrhal processes, the latter frequently associated with formation of concretions in the excretory ducts. If we can establish the coexistence clinically of diabetes, steatorrhea and azotorrhea in addition to a palpable enlargement of the head of the pancreas we should suspect an involvement of this organ. Unfortunately these symptoms are rarely present simultaneously. He finds that the most constant clinical sign is tumor in the particular abdominal lesion, that is, a swelling of the head of the pancreas; which means that phenomena of pressure resulting therefrom—for instance, compression of the pylorus, icterus, passive congestion in the portal vein system, ascites, and enlargement of the spleen, edema of the lower extremities, and celiac neuralgia—are provoked by pressure caused by increase in volume of the head of the pancreas. The differential diagnosis must consider the distinction from *catarrhal icterus*. A particularly stubborn icterus accompanying a palpable tumor in the region of the pancreas speaks for pancreatitis. An existing pancreatitis may simulate cholelithiasis. Here the following argument seems logical: Chronic and slowly increasing icterus with simultaneous colics, enlarged gallbladder, with symptoms of protracted cholelithiasis, and an olive green or yellowish discoloration of the skin, speaks for pancreatitis; especially so when at the same time a tumor can be palpated in the pancreatic region. If carcinoma of the pancreas can be excluded, and an operation produces improvement,

these consequent effects of the laparotomy confirm the diagnosis of chronic indurative pancreatitis.

*Adrenalin Glycosuria and Certain Relations between the Adrenal Glands and Carbohydrate Metabolism*, by C. A. Herter and A. J. Wakeman.<sup>19</sup> Application of adrenalin on the pancreas causes a stronger excretion of sugar than when this substance is brought upon the brain, liver, skin, or kidneys. In one case 24 gm. of sugar was excreted inside of 12 hours after the head of the pancreas had been painted 10 times with 1 cc. of a solution of adrenalin chlorid, 1 to 1,000. In adrenalin glycosuria the amount of sugar in the blood is regularly increased, thus differing from the phloridzin glycosuria. These authors incline to the view that the pancreas is the organ which is principally concerned in the development of adrenalin glycosuria, for in five dogs in which the pancreas was completely removed after bilateral ligation of the vessels of the adrenal bodies, the urine contained no sugar, or only a trace. Nearly all reducing substances, not the oxidizing substances, produced glycosuria when brought upon the pancreas. The second part of this work considers the relation of the adrenal bodies to carbohydrate metabolism. Compression of the adrenals causes glycosuria, their extirpation causes diminution of the sugar in the blood.

Similar experiments on the spleen were negative. If adrenalin was brought into the abdominal cavity considerable time after the extirpation of the suprarenal bodies the glycosuria did not occur. We shall return to this subject in considering Professor Reginald H. Fitz's paper.

*Pancreatic Disease Simulating Cholelithiasis*.—Since the work of Opie, the physiologic, embryologic, and pathologic relationship between the pancreas and liver has been more carefully studied. Worobjew<sup>20</sup> also emphasizes that the pancreas frequently participates in diseases of the liver, and what is more important to know, it may closely simulate hepatic disease, particularly cholelithiasis. A complete clinical picture of gallstones may thus be present, due exclusively to chronic disease of the pancreas. Infrequently, also, both organs are affected, and we have reasons to surmise that the classic symptoms of biliary calculi are only in part due to the latter, the pancreatic component entering largely into the clinical picture. For the physician, and still more so for the surgeon, these facts carry the greatest weight. It has occurred that an operation was performed for "gallstones," and stones were removed from the gallbladder,



yet no improvement resulted, and at the autopsy calculi were discovered in the pancreas. Symptoms pointing to pancreatic involvement (chronic inflammations, calculi, etc.) are: 1. Colicky pains in the left hypochondrium, unaccompanied by jaundice. 2. Diabetic manifestations, chiefly rapid emaciation. 3. Fatty evacuations. 4. Salivation. 5. Tumefaction and resistance in the region of the pancreas. 6. The appearance of calculi in the stools following attacks of colicky pains, the calculi consisting of carbonates and phosphates of lime. As to treatment, narcotics are of small value in pancreatic colic. Pilocarpin, hypodermically and pancreatin internally, deserve a trial, but in the event of failure, recourse should be had to surgical measures.

Steinhaus<sup>21</sup> reports autopsy findings in 12 cases of cirrhosis of the liver. In 11 of these, chronic interstitial inflammation of the pancreas was found. The character of the inflammation is not described with the same exactness that Opie gives to this subject. It is said to be a chronic interstitial inflammation of the pancreas, similar in each case to the condition found in the liver of the same subject. The islands of Langerhans were found affected in only one case. The diminished tolerance for sugar frequently observed in cirrhosis of the liver is, therefore, probably due to the implication of the pancreas and not to the liver condition. It is not necessary to classify separately the glycosurias accompanying cirrhosis of the liver, arteriosclerosis, pancreatic disease, etc. Rather, it is to be inferred from all recent investigations that every case of glycosuria is probably due to some disturbance in the functions of the pancreas, and that this organ alone controls the carbohydrate metabolism of the organism.

In recent American literature, two cases of pancreatitis, due to preceding cholelithiasis, are reported; one of acute pancreatitis with fat necrosis, by G. H. Monks and David B. Scannell, terminated fatally after the operation. The pancreas and the left suprarenal body were disintegrated by fatty necrosis. The second case was one of chronic pancreatitis, and is reported by Harding.<sup>22</sup> It occurred in a woman of 49, who had previously had both breasts removed for cancer. The symptoms came on acutely, and consisted of severe pain in the epigastrium, lasting for four hours. Attacks of pain occurred every third day, associated with fulness in the stomach and frequent eructations of gas; jaundice, nausea, constipation and neurasthenic symptoms were present.

At operation, the pancreas was found enlarged and nodular, which led to the suspicion of cancer. A small piece of the pancreas was examined, but showed simply chronic pancreatitis, and no cancer. Nothing was done, except to open and drain the gallbladder, and the patient recovered entirely. Both of these recent cases from American literature emphasize the necessity of exploratory laparotomy as soon as such conditions are suspected.

*Relation of the Pancreas to Diabetes and Glycosuria.*—Medical literature bearing upon this relationship in the past year has been very prolific, but it cannot be said that the various publications on this subject have distinctly advanced our knowledge. Professor Ribbert, in his excellent textbook on "Special Pathology, etc.," emphasizes that although destruction of the pancreas may cause diabetes in man and animal, there are cases of diabetes, on the other hand, in which no affection of the pancreatic tissue is apparent. This may find its explanation in such very slight degenerative changes of the pancreatic cells that they cannot be recognized even by the microscope; but on the other hand, it might be explained by the fact that there undoubtedly are forms of diabetes having a different anatomic substratum, not dependent on pancreatic changes. Pavy defined diabetes as a disease in which dextrose is present in the blood and urine, and in which ultimately levorotatory betahydroxybutyric acid appears in the blood and urine, and the output of carbohydrates in the urine is greater than can be accounted for by those in the food. Dr. Pavy, many years ago, pointed out that a diabetic patient who was on a strictly carbohydrate-free diet may, if a little carbohydrate be given, excrete far more sugar than that given in the food. In connection with this historic observation of Pavy, Dr. W. Hale White,<sup>23</sup> in a symposium at a meeting of the Chelsea Clinical Society, suggested that experiments might be made to see whether diabetics can utilize other forms of sugar, for he found that they may utilize levulose better than dextrose. He argued that information was needed on the three following questions: (1) Is alteration of the islands of Langerhans the essential feature of pancreatic disease which causes diabetes? (2) Can we tell during life which patients have and which have not diabetes? (3) What is the relationship of internal pancreatic secretion to diabetes?

To answer these questions in the reverse order in

which they are placed, and answer them from recent literature, I would have to say, basing my remarks on the work of Herter and Wakeman,<sup>19</sup> and the book by Ribbert, as well as from deductions made from the symposium on pancreatic disease before the Association of American Physicians, Washington meeting, May, 1903, that the idea of an internal secretion of the islands of Langerhans is not yet sufficiently well grounded to justify reliable conclusions. The second question, whether during life we can tell which patients with diabetes have and which have not pancreatic disease, cannot be answered except by exploratory laparotomy. The first question is best answered by the following work of Weichselbaum and Stangl.

*Histologic Examination of the Pancreas in Diabetes Mellitus.*—Weichselbaum and Stangl<sup>24</sup> report 32 cases of diabetes, in all of which they made studies on the pancreas with especial reference to the islands of Langerhans. They found the pancreas diseased in all cases, but the changes affecting the islands of Langerhans were especially marked and constant. These alterations concerned the number, size and structure of the islands. There was diminution of their size and number in all the cases, but in addition they were affected by one or more of three special changes: Simple atrophy of the epithelium, vacuolization and liquefaction of the epithelium, and sclerosis of the islands; occasionally hemorrhage and calcareous infiltration were also present. All of these changes, however, led to diminution of size and ultimate destruction. The alterations in the parenchyma of the pancreas were neither constant nor ever sufficiently marked to be considered of primary importance. The lesions included atrophy of the tubules, proliferation of the central acini, increase in the amount of interstitial connective tissue, interstitial pancreatitis, both acute and chronic, fat necrosis, lipomatosis, cirrhosis of the pancreas, and atheroma of its arteries. Their results correspond very closely with those of other recent observations. The authors believe that the parenchymatous alterations and those in the islands of Langerhans are entirely independent of each other. While they are not positive in the statement that the changes in the islands of Langerhans cause diabetes, still they believe that the evidence gathered by themselves and others is in favor of the existence of such a causal relation. In addition to the pathologic changes mentioned they base their opinion on the facts that the alterations in the

islands of Langerhans have never been observed in other diseases; that cases in which pancreatic disease exists without change in the islands of Langerhans are nondiabetic; that these changes are constant in diabetes, the alterations in the rest of the pancreas are not; and that as the two parts of the pancreas are so different in their development and structure, it is likely that they also vary in their function.

In the debate on diabetic and nondiabetic glycosuria, Saundby<sup>25</sup> defined these conditions as follows: Diabetic glycosuria is a glycosuria in which assimilation fails; and nondiabetic glycosuria is that in which assimilation is not at fault; and J. Rose Bradford said that many distinct and separate forms would be recognized in future, and although the presence of glycosuria was so intimately associated with diabetes, yet that disease might exist when no sugar was present. He suggested that five varieties of diabetic glycosuria might be described: (1) That dependent on disturbed function, of absorptive and other mechanisms of the digestive tract—the alimentary glycosuria. (2) Glycosuria of hepatic origin, abnormal glycogenic function of the liver. (3) Pancreatic diabetes. (4) Renal glycosuria based upon the experimental results with phloridzin, which caused glycosuria by action of the renal cells. (5) Diabetic glycosuria might arise as a result of primary disintegration of the tissues.

The form of glycosuria which can be produced by lesions of the nervous system, has only an experimental basis so far.

*Symposium on Pancreas and Pancreatic Disease* (Washington, May, 1903).—This symposium was led chiefly by E. L. Opie,<sup>26</sup> of Baltimore, on the anatomy and histology which I have already abstracted. A second paper was the physiology and physiologic chemistry by Prof. R. H. Chittenden, of New Haven, who dwelt upon the two distinctive functions of the pancreas. He referred to the work of Bayliss and Starling who had separated from the duodenal mucosa a substance which they call “*secretin*” upon which the secretion of the pancreatic juice depends. I wish to remark that these researches of Bayliss and Starling have recently been confirmed by two French experimenters, Enriquez and Hallion<sup>27</sup> who extend the physiologic effects of secretin, and assert that it is not a specific stimulant for pancreatic secretion, but also stimulates the secretion of bile. They also assert that



an acid, as well as sodium bicarbonate, two antagonistic chemicals (acid and base) will produce an abundant flow of bile and pancreatic juice, when brought upon the mucosa of the duodenum in dogs that have a duodenal fistula. Chittenden does not furnish in his report satisfactory evidence that the cells of the islands of Langerhans have an internal secretion. The cells of the pancreas have more pentose than the other cells in the body. Chittenden called attention to the results of Herter and Wakeman concerning the adrenalin glycosuria, and the reducing action upon the pancreatic cells. The fact that many organs of the body might form reducing substances which might reach the pancreas in the blood stream, made probable that in this fact was to be found a new light on the origin of diabetes. However, Herter and Wakeman<sup>28</sup> found that not only reducing substances but also oxidizing substances could cause glycosuria. Adrenalin when brought upon brain, liver, spleen or kidney, also produces increased excretion of sugar, and they could not positively prove whether or not this adrenalin had been absorbed into the general circulation and after all produced its effect by acting upon the pancreas, for to decide this it would have been necessary to extirpate the pancreas, a procedure which in itself inevitably causes glycosuria. So the present state of the physiology of the pancreas gives us no new and precise information on these important questions.

The experiments of Herter and Wakeman would receive a new interpretation if the statements of Poehl<sup>29</sup> could be confirmed, concerning the derivation of the poison known as adrenalin. Poehl asserts that this substance does not by any means occur only in the adrenals, but in all other organs and tissues of the body. He attributes the priority of having discovered adrenalin in 1892 to Kondratiew, who it is claimed made a strong solution of it from the spleen of animals. So long as the adrenalin is in the nucleus of the cells, it is not only harmless, but of advantage to the organ. The poison leaves the cell, according to Poehl, when the juices of the organism become acid, which can occur from certain forms of anemia and diabetes. To avoid this extrusion of the poison from the cells, the alkalinity of the juices must be restored.

The report on the etiology and pathologic anatomy of pancreatic disease made in the foregoing symposium, by Simon Flexner, contains nothing new outside of what E. L. Opie has contributed on this subject in the *Journal*

of *Experimental Medicine*, namely, that there are two forms of chronic inflammation of the pancreas, an interlobular and an interacinar form, and it is the latter form which is the one associated with diabetes.

The most valuable paper from a clinical standpoint that was contributed to the symposium was that on the symptomatology and diagnosis of disease of the pancreas, contributed by Prof. Reginald H. Fitz,<sup>30</sup> who began by a reference to the work of Friedreich,<sup>31</sup> in 1875. According to Friedreich, no single symptom which may occur in diseases of the pancreas is a pathognomonic, and the occurrence of several does not always result in a positive diagnosis; fatty stools, melituria, epigastric pain, with the characteristics of celiac neuralgia and palpable tumor, lead among the symptoms most useful in diagnosis, and then follows a remarkable statement of Friedreich, which I have, since his publication, occasionally seen erroneously attributed to others, viz.: "The presence of undigested striated muscle fibers in the feces is worthy of every consideration, and may prove of diagnostic value." Fitz agrees with other authorities that the symptoms and signs especially suggestive of pancreatic disease are dependent largely upon the resulting disturbances of (1) its functions, and (2) upon the physical condition and situation of the organ. The former include the various modifications in the composition of the urine and feces, the latter comprise the localized resistance, tenderness and pain, and the evidence of obstruction of the gastrointestinal and biliary tracts. The demonstration of sugar in the urine, of visible fecal fat, or undigested muscle fibers in the feces, often led to the assertion that pancreatic disease was present when one or more of these conditions had been determined. But when the results of clinical observation were compared with anatomic investigation, it became evident that diseases of the pancreas occurred much more frequently without the recognition of glycosuria, and excessive fat and muscle in the feces than when these abnormalities were evident. If diabetes is associated with long-continued bronzing of the skin and enlargement of the liver, in the absence of jaundice and the characteristic distribution of the pigment in Addison's disease, the suggestion is direct that chronic fibrous pancreatitis is present. Anschütz has tabulated 24 cases of complication since the original publication by Hanot and Chauffard on this subject (the bronzed diabetes of the French writers).

In this paper by Fitz there is a table showing the relation between visible fecal fat, jaundice, and pancreatic disease. Only those cases are included which gave anatomic changes at autopsy, a laparotomy, or by passage of a pancreatic calculus, that there was actual disease of the gland. Without going into details of figures, the table suggests that in about three-fifths of the cases of steatorrhea attributable to pancreatic disease there was neither diabetes nor jaundice; that in two-fifths there was either diabetes or jaundice in about equal proportions, and in but few instances was there a combination of diabetes and jaundice. In another table the view of Müller is brought out that in pancreatic disease there is less splitting of fat, and consequently an increase in the neutral fat, thus giving a satisfactory explanation of the oily stools of older writers. This is not the case without exception, however. The possibility that the feces may contain an excessive amount of fat occurs not only in cases of jaundice, but also when there is superabundance of fat in the diet or when there is an abnormality of the absorptive function within or without the intestinal wall. Steatorrhea is therefore to be regarded as an evidence of disease of the pancreas only when other causes for its presence can be excluded, the most important of which is interference of flow of the bile into the intestine.

Fitz emphasizes that any disturbance in the digestion and assimilation of fat, muscle, and carbohydrates from affections of the pancreas has almost invariably been connected with extensive and protracted lesions. It is obvious, therefore, that feeding with an increased quantity of one or the other of these constituents of diet in suspected cases of pancreatic disease might be followed by appreciable changes in the secretions and excretions earlier than otherwise would have been the case. It is clear, also, that deficiency in the digestion of fats, starches, and proteids, relieved by the addition of pancreas or its preparations to the diet, provided disease of the remaining digestive glands could be eliminated might furnish additional evidence in favor of the pancreatic source of the disturbance.

Regarding the dietetic experiment of testing the functions of the pancreas, Fitz favors the view that aims to increase the quantity of fat in the diet nearly to the limit which can be reached without producing steatorrhea in healthy persons or in patients not suffering from disease interfering with the absorption of fat. It

would be particularly desirable to know the toleration of fat in those cases of diabetes in which the pancreas presents no abnormal condition. These methods require the trained physiologic chemist. In a like manner the capacity of the patient for digesting muscle fiber in the intestine as compared with that of a normal individual should be tested. Of course this would necessitate that we should first know the condition of the gastric function, and that we should introduce into the intestine muscle fiber as free as possible from the influence of gastric digestion.\* We shall refer to a more practical method suggested by Adolf Schmidt<sup>38</sup> at the end of this article.

The efficiency of the pancreas for digesting the starches might be tested by an experimental alimentary glycosuria. The salol method of Ewald and Sievers, and the glutoidiodoform capsules of Sahli are chemic methods of doubtful efficacy in the diagnosis of pancreatic disease. Yet one is justified in concluding that the secretory functions of the pancreas are normal whenever the iodoform (iodin) reaction in the saliva occurs within 3 to 4 hours of swallowing the capsule, but a delay in this reaction up to even 12 hours does not warrant the conclusion that there is an insufficient secretion of pancreas. Opie<sup>32</sup> has suggested the possibility of discovering in the urine the fat-splitting ferment set free in acute pancreatitis. He endeavored to determine its presence in one case by following the method proposed by Kastle and Loevenhardt, which is based upon the decomposition of ethyl butyrate by lipase and the production of butyric acid. The urine neutralized with potassium hydroxid was divided into two portions, one of which was boiled for the purpose of destroying the ferment. Ethyl butyrate was added to each specimen. That unboiled after 24 hours gave an acid reaction, while the boiled specimen showed little if any change. It is necessary, however to know prior to accepting any conclusions from this test, whether normal urine does or does not contain *lipase*.

The symptoms which have proved most useful in the diagnosis are those which call attention directly to the region of the pancreas. They are epigastric pain, tenderness, tension and tumor, with or without obstructive jaundice, and evidence of mechanical interference with the motility of the stomach and duodenum. Although the diagnosis of diseases of the pancreas in the light of

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\* Ground meat pulp might be introduced into the duodenum by Hemmeter's or Kuhn's method of duodenal intubation.



our present knowledge depends practically more on the symptoms calling attention to the locality of the organ, than upon the evidence of disturbance of its function, it is reached eventually by the exclusion of other sources than the pancreas, as causes of the local symptom. Fitz in his first publication on acute pancreatitis (1889), emphasized that the symptoms are essentially those of a peritonitis beginning in the epigastrium, and occurring suddenly during ordinary health without obvious cause. The diagnosis is based on the pain, tenderness and tympany limited to the region of the pancreas, and on the gradual development of deepseated peritonitis. The differential diagnosis lies practically between an irritant poison, perforation of the digestive or biliary tracts, and acute intestinal obstruction. In cases of acute pancreatitis thus far reported, no new evidence has been furnished which gives to the diagnosis more than a variable degree of probability. Certainty has been reached only by laparotomy or a postmortem examination. Fortunately exploratory laparotomy has proved the most satisfactory method of treatment for relief of acute symptoms in an increasing number of cases.

The diagnosis of *chronic* pancreatic affections is based on the occurrence of localized pain and presence of tumor; the evidences of disturbed pancreatic function are to be sought along the lines previously mentioned, but experience has shown that definite and convenient additions to our knowledge, are necessary before functional disturbances of the pancreas can be ascertained sufficiently early and with sufficient certainty to render assured the pancreatic source of the disease. Such personal efforts I shall describe in the following:

*Fat Necrosis.*—Gideon Wells<sup>33</sup> gives the results of his experiments on fat necrosis as follows: 1. Fat necrosis seems to be merely a special form of necrosis of fat tissue, differing from simple necrosis chiefly in the sharp limitation of the affected area, usually by a wall of leukocytes, and later by connective tissue; and the filling of the necrosed cells by the products of fat splitting. Each of these features can be produced experimentally in various ways, but the complete picture has never yet been produced except by products of the pancreas. 2. Fat necrosis can be produced with constancy in cats and dogs, less successfully in rabbits, by intraperitoneal injections of extracts of fresh hog pancreas, and nearly as well with dog pancreas. The results are the same with solutions that are in weak alkalies ( $\text{Na}_2\text{CO}_3$ ), weak acids

( $\text{NH}_4\text{COOH}$ ), or in water. Fat necrosis produced in this way is the same in appearance, both macroscopically and microscopically, as human fat necrosis. 3. Equally constant results can be obtained with ordinary commercial "pancreatins." 4. Preparations of carica papaya, although highly irritating, do not produce fat necrosis. 5. This property of pancreatin to produce fat necrosis survives for five minutes at a temperature as high as some point between  $65^\circ\text{C}$ . and  $71^\circ\text{C}$ .; above this point the property is entirely lost. The amount of fat necrosis produced decreases steadily after exposure at  $55^\circ\text{C}$ . and upward. These observations point to enzyme action as the source of the condition. 6. It has been impossible to ascertain which of the pancreatic enzymes causes fat necrosis.

Pancreatin, weak in or devoid of lipase, will not produce this effect. Lipolytic extracts of hog's liver or cat's serum are likewise inactive. Mixtures of lipolytic extracts of liver with pancreatic trypsin will not produce fat necrosis. Extracts of fresh dog pancreas that are, when injected, feeble in or devoid of tryptic power, but possess lipolytic power, cause fat necrosis. If to such extracts an emulsion of duodenal mucosa is added, the enterokinase greatly increasing the tryptic activity, no fat necrosis will be produced. As the lipase of pancreatic extract cannot be isolated, it is impossible to ascertain if it by itself is capable of causing fat necrosis; but it seems highly probable that it is essential. It may be that the lipase causes fat splitting after some other ingredient of the pancreatic juice has injured the cell. 7. When fat tissue within the body has been made necrotic and preserved from outside influences of absorption, etc., the lipase that it may contain does not produce the change of fat necrosis. 8. Simple alkaline solutions of the strength of pancreatic juice or slightly stronger ( $\text{NaOH}$ ,  $\text{Ca}(\text{OH})_2$ ,  $\text{Na}_2\text{CO}_3$ ), do not produce fat necrosis. 9. Many of the features of fat necrosis may be produced after death in animals, and also in vitro, with pancreatin, but the resulting condition does not resemble fat necrosis at all closely. 10. Dissemination outside the abdominal cavity has been observed as early as 12 hours after intraperitoneal injection. The route by which the spreading is accomplished is probably the lymphatic system. 11. The forms of the foci produced seem to depend simply upon the area exposed to the action of the pancreatin. 12. The earliest change in fat necrosis is a simple necrosis of the surface tissue, which extends

gradually into the deeper fat cells. Fat splitting is subsequent to the necrosis, and not its cause. At first the products are noncrystalline, but become crystalline later. 13. The process progresses for but a few hours at any one point, the extension seeming to be limited by the surrounding leukocytes. Absorption of the area is accomplished by leukocytes, and healing is by proliferation of connective tissue from the margins. Adhesions are seldom formed. 14. The foci become visible to the naked eye in three to five hours. They may disappear within 11 days, or persist for a much longer time, depending chiefly upon their size. 15. Fat necrosis by itself is not dangerous to the affected animal, and may develop while the animal shows no observable symptoms.

*Prospects of Diagnosing Pancreatic Insufficiency from Defective Proteolysis, Amylolysis, and Adipolysis.*—The difficulties besetting deductions from defective proteolysis have already been considered, and concerning the amount of fat that appears in the feces undigested (defective adipolysis) the results would be misleading, unless we knew how much fat the intestinal wall regularly excretes into the fecal mass. In the feces of a person under starvation diet (that means the feces which appeared when no food at all was taken for several days) F. Müller<sup>34</sup> found from 26.3% to 35.46% of fat (in the dried feces), and Rubner found in the feces of a subject kept on an entirely fat-free diet 3.1 gm. to 6.5 gm. of ether extract a day. If these are the amounts of fat found in feces when no fat is taken in diet, it is logical to assume that much more is to be found when the diet contains moderate or abundant quantities of fats. Then there are great variations in fat digestibility that are dependent upon (1) the digestive or adipolytic power of the person under observation; (2) the digestibility of the fats, which is inversely proportional to their melting points. The higher the melting point, the less fat will be absorbed, and the more will appear in the feces. When the same quantities of stearin, mutton fat and olive oil are ingested, the amounts were determined as lost in the feces: Stearin, 86% to 91%; mutton fat, 7.4% to 9.15%; olive oil, 2.3%.

In looking about for some practical chemie method to facilitate the diagnosis of pancreatic disease, I entertained the hope that by careful qualitative and quantitative methods I might be able to determine the "threshold" of fat digestibility, and by repeated analyses of feces after ingestion of weighed amounts of fats, I might be able to

ascertain approximately just how much fat an adult of known size and weight could digest, and determine the time when I would have a right to expect to find the fats excreted in the feces. Here we meet with almost unsurmountable difficulties, because to be of value, the "threshold" will have to be determined for each patient individually, and to experiment upon a sick person with ever-increasing fat diet is impossible. These aims to determine a limit of fat digestibility and absorbability, and what I might call a relative "pancreatic insufficiency," are in my opinion not feasible. It is only when the analyses for fecal fat show very decided increase of fat lost that this factor becomes available for diagnosis. Evidently this can only occur when the ducts of Wirsung (and Santorini) are completely stenosed, or when the pancreatic cells have undergone advanced degeneration. For an early diagnosis, even such analyses are not helpful.

*Defective Amylolysis and Its Significance.*—As a measure of intestinal amyolysis, we use test-meals made of potato puree or of well-boiled rice. Under normal conditions none of the ingredients of the stool should show a blue reaction with iodine after such a diet. Any cells of potato which may assume a pale violet color are, as a rule, found to be still retaining their cellulose envelope to a large extent. Now, defective starch digestion as shown in the stool does not in practice permit of a deduction concerning the condition of the pancreas. Defective starch digestion depends, in a great majority of cases, upon a disturbance of the secretion of the succus entericus. If, instead of the microscope, in testing for undigested starch, the fermentation test of Adolph Schmidt is used, it must be emphasized that only the positive occurrence of extensive fermentation is of diagnostic value, for the deduction is not logical that starch digestion is normal when there is no abundant evolution of gas. For it is possible that the carbohydrate fermentation may be submerged under a more active putrefaction of proteid, and in fatty stools there may be formation of abundance of acid product without gas development (Adolph Schmidt<sup>85</sup>).

*Nondigestion of Nuclei in Meat Fiber a Criterion of Pancreatic Insufficiency* (Test of Adolph Schmidt).—It is known from the interesting investigations of Adolf Schmidt<sup>39</sup> that raw connective tissue can only be digested by the gastric juice, while the nuclear substance of meat fiber can only be digested by pancreatic juice. Hence the appearance of remnants of undigested connective



tissue in the feces points to insufficiency or absence of gastric secretion; and the appearance of nuclei of cells in meat fibers is significant of insufficient secretion of pancreatic juice. Personally, I have tested the first deduction of Schmidt's on eight cases of achylia gastrica and six cases of chronic atrophic gastritis with entire absence of free or combined HCl and ferments. In all eight cases of achylia gastrica, and in five cases of atrophic gastritis the undigested connective-tissue fibers were found in the feces. In two cases of heterochylia (*i. e.*, variable gastric secretion—hyperchlorhydria with excess of pepsin and chymosin alternating with absolute achylia in the same person after the identical test-meal.<sup>40</sup> The undigested connective-tissue fibers were found in the feces only during the periods of absolute achylia, when the gastric juice contained no free or combined HCl. They disappeared from the feces in periods during which the gastric juice was normal.

Two of these cases of heterochylia I have had under observation off and on for eight years. Their feces and gastric contents were examined during a period of five to six weeks in the spring and fall of each year. I might add that during the periods of absence of HCl and enzymes in the gastric juice, no biuret reaction could be obtained in the gastric filtrates, but that the addition of 10 cc. of officinal dilute hydrochloric acid, together with 1 gm. of pepsin, diluted with distilled water to represent the concentration of HCl in gastric juice, caused perfect digestion of connective tissue, if persisted in for 48 hours; that is, at 0.2% (two per mille) solution of HCl, with sufficient pepsin to approximate the concentration (amount) in gastric juice, will cause disappearance of undigested connective-tissue fibers from the stool. The amount of pepsin to be added varies with different patients and with different meals, but cannot be definitely stated *a priori*. It should be added to the gastric filtrate or chyme (10 cc.) until the reaction of free HCl appears on titration with Congo and the phloroglucin-vanillin test. Sometimes it is impossible for the patient to swallow such large quantities of dilute HCl. Then we occasionally succeeded by giving the requisite amount of officinal HCl in large gelatin capsules, and directing the patient to drink the corresponding amount of water afterward.

For studying the condition of the pancreatic secretion by means of its effect upon the nuclear substance of meat fiber, Ad. Schmidt uses slightly fibrous beef, which is

cut into small cubes of 0.5 cm. square and preserves them in absolute alcohol. After they are hardened they are placed in very tiny sacs made of silk gauze and placed in alcohol. Prior to using them as tests they are immersed in water for three hours and given to the patient in wafers. The test-diet which Schmidt recommends<sup>41</sup> must be faithfully adhered to and does not impose any inconveniences upon the patient. Personally, I make use of an improved Boas stool sieve for regaining the little silk sacs. If the patients have any pancreatic disturbance there must of course be remnants of muscle tissue in the sacs. In the sifted stools of 12 healthy students, no muscle remnants were ever found in 30 different tests. If muscle remnants are found they are washed in water, hardened in alcohol, sectioned if need be, and stained with nuclear stains. It is not, as a rule, necessary to harden the beef remnants; after rinsing them in water they can be directly treated with oil acetic acid or methyl-blue. Wallenfang studied these beef remnants after they had passed through the entire digestive tracts of dogs that had been deprived of the pancreas. In three dogs that survived total extirpation of the pancreas, the meat fibers regularly contained their nuclei and were readily stainable.

Preservation of the nuclei justifies the conclusion of pancreatic disease or at least absence of pancreatic juice from the intestine (the two conditions are not always identical) only—if the time of the passage of the meat was of a normal period. A very rapid passage of the sacs such as occurs in diarrhea frustrates the action of the trypsin, even if it is present.

In two cases of pancreatic abnormality this test worked satisfactorily. One was a large pancreatic cyst compressing and obliterating the duct of Wirsung, a second case was stenosis and adhesion of this duct by an old pericholecystitis an extension of a preceding cholelithiasis. In the first case the pancreas itself did not appear seriously diseased at the operation, it seemed that its entire secretion was collected into the huge cyst, the contents of which had the same physiologic and chemic properties as a similar case closely studied by me in 1898.<sup>42</sup> Both patients recovered after operation and six weeks thereafter no nuclei could be discovered in the stools. Adolf Schmidt believes that his test, when combined with the test of Sahli, will facilitate the diagnosis of pancreatic diseases, and if I may speak from my

rather limited experience thus far, it must be in confirmation of his conclusion.

It has suggested itself to me that instead of looking for undigested residues of a meat diet with the microscope, we might determine the amount of total nitrogen in the feces, and from this the caloric value after a diet of a weighed amount of meat. Here, we would, however, meet a new difficulty, and that is of confounding defective proteolysis (imperfect meat digestion) with defective absorption, for the feces may show no undigested meat fibers whatever after a meat diet, and yet with the Kjeldahl method of determining the total nitrogen it can be demonstrated that the dried feces may contain from 8% to 10% of nitrogen, and that its ether extract may be from 11.5% to 13.5%. One gram of nitrogen of the feces, after they have been freed from fat and incinerated, corresponds to 45.4 calories; and after a weighed meal of meat given to dogs, it has been found that the nitrogen in the feces may be equal to 5,900 calories. These are deductions from the experiments of Frentzel and Schreuer, made upon dogs, but the same is true of the human feces, and the more meat is ingested in the diet the greater will be the percentage of nitrogen in human feces, and in enteritis the amount of nitrogen increases in proportion to the destruction of the mucosa. There may be larger amounts of nitrogen in the feces, and yet no undigested beef residues can be found with the microscope. This does not point to imperfect digestion, and permits of no deductions concerning the pancreas. It is pathognomonic of imperfect absorption. All chemic tests concerning the occurrence of undigested proteid, carbohydrates and fats in the stool, and their relation to pancreatic diseases, have a limited value when taken in conjunction with the physical signs, the anamnesis (icterus, cholelithiasis, hepatic colic, etc.) and the results of examination of the urine.

As these methods, however, are the most promising ones for furnishing new aids to diagnosis of pancreatic diseases, there must be no cessation in the progress of such investigations. Eventually we may find the one helpful and reliable method of diagnosis. As Hippocrates says in one of his aphorisms: *Ὁμὲν βίος βραχὺς ἡ δὲ τέχνη μακρά* ("Life is short, but art is long.")

For most of our diagnostic methods of the present, our mental attitudes may be expressed in the words of Goethe's Faust:

O glücklich, wer noch hoffen kann,  
Aus diesem Meer des Irrthums aufzutauchen!  
Was man nicht weiss, das eben brauchte man,  
Und was man weiss, kann man nicht brauchen.

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A very curious impression is made upon the objective [165] investigator to see the scientific judgment obscured by ill-guided patriotism. No less than four monuments have been erected in three different countries to perpetuate the memory of four different discoverers of the circulation of the blood. The Spaniards regard Michael Servetus, born in Villanueva in 1511, as the discoverer of the circulation, and have erected a monument in the Museo Anthropologico at Madrid. The Italians have three men to whom the title to this discovery is accredited with more or less historic and scientific correctness, namely: Matheus Realdus Colombus, born at Cremona in 1516; Carlo Ruini, of Bologna;<sup>1</sup> Andreas Cesalpinus, born at Arrago in 1519. Monuments have been erected to Carlo Ruini at Bologna and to Andreas Cesalpinus at Pisa and Rome. William Harvey has been honored by a monument in London erected by the Sydenham Society, a second at Hempstead, and a third at Folkstone. This makes five discoverers in all, but there is one more. The French have claimed the discovery of the circulation of the blood, and their

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<sup>1</sup>Book on Anatomy and Diseases of the Horse, published in 1598, in which Ruini gives the unmistakable evidence that he had grasped the action of the cardiac valves.



[165] discoverer is that incomparable satyric François Rabelais, and this assertion is made by no less than Paquelin.<sup>2</sup> But a critical study of the passages from Rabelais, which Paquelin cites, proves that the alleged French discoverer brings nothing new, nothing which was not already stated by Galen, that he nowhere mentions dissections or vivisections as basis for his claims.

The department of physiology which was most fatally retarded in its progress by a defective knowledge of the ancients is that concerning the circulation of the blood. In the Lane lectures, delivered at Cooper Medical College, San Francisco, in 1900, Sir Michael Foster has given us an admirable review of the history of the circulation of the blood. These lectures constitute a most scholarly and inspiring addition to our knowledge of the subject. The first and second chapters of this book treat of the circulation, especially the second chapter. The first chapter does not treat of the circulation directly, but of Vesalius, his forerunners and followers. In narrating the contributions of the Italian physiologists and anatomists, there is this difference between the tenor and spirit of presentation by Foster, and that by Spanish and Italian medical historians. Foster leaves us under the impression that the Italian physiologists and anatomists made no contributions or discoveries of enduring excellence or genuine scientific merit, whereas the Italian historians<sup>3</sup> make every effort to convince us that the work of their fellow-countrymen constituted solid building blocks in the architecture of physiology; that their

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<sup>2</sup> *Revue de Litér médic*, 1878, p. 499.

<sup>3</sup> See Luigi Luciani, *Physiology of Man*, at present being translated into German by Baglioni and Winterstein: § G. Ceradini. *Ricerche storico-critiche intorno alla scoperta della circolazione del sangue*, Milano, Fratelli Rechiedei, editori, 1876. *Difesa della mia Memoria intorno alla scoperta della circolazione, contro l'assalto dei signori H. Toll in teologo in Magdeburg, e W. Preyer fisiologo in Jena. Con qualche nuovo appunto circa la storia della scoperta Medesima.* Genova, tip del R. Istituto Sordo-muti, 1876.

For further literature on this subject see list at end of this article: "Literature on the History of the Discovery of the Circulation of the Blood."

conclusions were based upon precise and accurate observations [165] and experiment, as far as such were possible in those days. In order to judge with what justification the claims of the Italian authors are made, and also to judge of the critical conservatism and broad experience of Sir Michael Foster, a brief and critical review of the main contributions of the more renowned Italian workers in physiology and anatomy, and of Harvey, becomes indispensable.

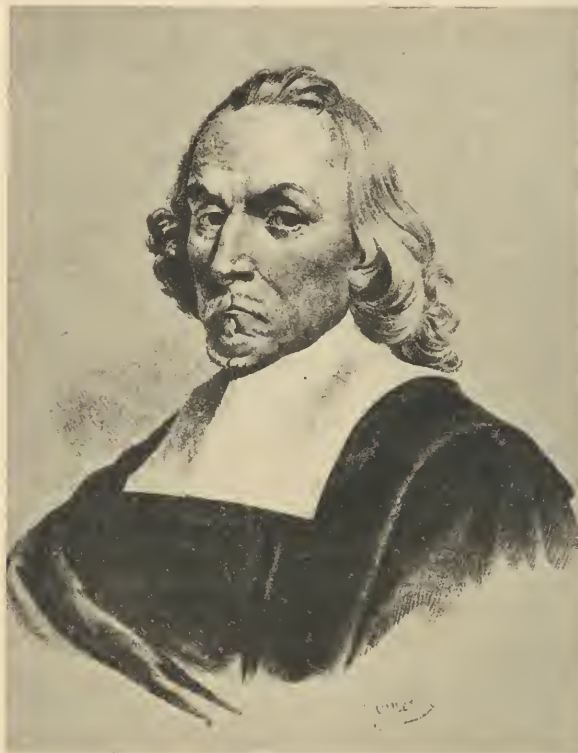
In the "*Deutsche Rundschau*," Helmholtz<sup>4</sup> credits poetic genius with the power of reviving long-past historic personages and transactions, and clothing historic characters not only with flesh and bone and garments, but with exactly portraying their psychic individuality and real personality. At the same time there is also an exact probing of the plausibility of the existence of certain characters. We can see this in the Thalmud connoisseurs, some of whom, of Jewish creed, have denied that Job and Jonah ever existed, and upheld other characters of the Old Testament as real personages. One has to be a very thorough, patient, persistent, and judicial student of any great historic character in order to successfully think oneself into the life and work and individuality of the person.

This is true in the study of the lives of Michael Servetus, Vesalius, Harvey, and others; it is not sufficient to read their history,—one must repeatedly sink one's psychic self into the life and period of the personage to be studied. Medical history writing, unless the writer and student has sunk his soul into the soul of the character to be studied, unless he has become part and parcel of the life and work, individuality, and even the social, scientific, religious, and political condition under which that character developed and produced his [166] results, has little value for an analytical mind.

In order to present a medical character justly and as correctly as possible, it is necessary to become a connoisseur of that character, and all the conditions influencing and surrounding him. We thus are even now able to recognize specialists on Galen, Vesalius, Servetus, Harvey, just as there

<sup>4</sup> Goethe's *Wissenschaftliche Thätigkeit*.

[166] are music lovers who are specialists of the compositions of Rameau, Paganini, Bach, Mozart, Beethoven, Chopin. Musical notes as printed are only the skeleton of music. Note-reading and mechanical technique will never make an artistic player. "He is not a correct interpreter of a composer until he puts his soul into it."



GUILLAUME HARVEY, 1578-1657 A. D.

This identification of the subjective powers of an artist with the work and musical nature of the composer, resurrects the composer before the mind's ear and eye of the performing artist. He begins to realize the subjective and objective peculiarities and becomes familiar with the train of thought and musical feeling that prompted the composition.

Similarly the mere reading of biographies and personal his- [166]  
tories of distinguished anatomists and physiologists, without  
a calm, self-possessed and patient analysis of all the collateral  
sources of information, will not give a picture of life-like  
distinctness. It is like playing the notes of a composer me-  
chanically in the absence of a wide reach of innate musical



MICHAEL SERVETUS, 1511-1553 A. D.

gifts. What is needed in medical biography as well as in  
the reproduction of classical music is the focusing of the  
entire mental energy of the writer upon the historic or musical  
problems in hand,—reading the literature in its original  
sources, and not from abstracts or quotations second-hand,  
and eventually, if possible, to combine the facts and data



[166] from all sources of information into an organic life-like whole, making the character and his times comprehensible to our modern methods of thinking.

The history of the discovery of the circulation of the blood begins with Galen (125-201 A. D.), who by his vivisections exposed the error of the Alexandrine school under Erasistratus (300 B. C.), who held that the left portion of the heart and the arteries were empty and that they, communicating by means of the small bronchi with the *arteria aspera* (trachea) served to convey the spirit of life (*pneuma*) to the various parts of the body, to animate them and that the veins alone contained blood with which to nourish the entire body.

Galen showed that one need only prick any artery or the left portion of the heart of a living mammal, in order to see blood gushing forth, which, in contrast with venous blood, was vaporous, thin, and "genuine," and which therefore consisted of a mixture of blood with the air inhaled in the lungs: "*mixtum quid ex ambobus.*"

According to Galen the left side of the heart is the center of the arteries, which through systole drives the *air-containing* (aerated?) blood (*sanguis spirituosus*) into all the organs, to animate them. The center of the veins on the other hand is the liver, from which the nourishing blood (*sanguis nutritivus*) is carried to all parts of the body by a kind of attractive and selective force. The blood from the right side of the [167] heart, from the *cava inferior*, goes for the most part into the left ventricle, through the pores of the septum (which Galen assumes, although he declares them to be invisible). In the left ventricle it becomes "spirituous" through mixture with *pneuma*, and through the aorta it is distributed over the entire body. However, a small portion of the blood contained in the right ventricle passes through the *vena arteriosa* (*arteria pulmonaris*) and then by way of the *arteria venosa* (*venæ pulmonales*) reaches the left ventricle.

Galen therefore had a notion, although imperfect, of the circulation of the blood through the lungs, and he knew that the venous vessels anastomose with the arterial ones, since he also had observed, that an animal might bleed to death from

a single artery. One point, however, in Galen's theory might [167] lead some critics astray in the explanation of the text. Galen assumed that the blood of the *arteria venosa* (*venae pulmonales*) flowed back into the lungs at each systole (through a sort of physiological insufficiency of the bicuspid or mitral valve), in order to exhale here the "soot" formed in the blood. Thus he assigned to the *arteria venosa* a double, and that an opposite, function, that is to say, first of conveying the reanimated blood from the lungs to the heart, and then again of conveying a portion of the same with the "soot"<sup>5</sup> from the heart to the lungs. Similarly Galen assigned to the *vena portae* a double function, in that he assumed that during digestion it conveyed the chyle to the liver, and when the intestinal canal is empty, it conveys the blood from the liver to the intestinal canal.

Certainly the two errors of the permeability of the septum and the systolic reflux dim, not a little, the splendor of Galen's theory of the lesser circulation; nevertheless it cannot be denied that Galen was the first to have a conception of the same, a fact which was recognized (long before G. Ceradini again drew the attention of investigators to it) by representative interpreters such as Harvey, Haller, Douglas, Maurocordato, and Senac, who referred especially to a passage in the 10th chapter of Book VI, "*De usu partium*," in crediting Galen with a conception of the respiratory circulation.

Let us now see who first corrected and completed the theory of Galen, by the rejection of the assumption of the permeability of the cardiac septum, and by the determination of the fact that not only a part, but all the blood driven out from the right ventricle reaches the left ventricle by anastomoses of the pulmonary vessels.

In the year 1553 the Spanish physician and theologian

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<sup>5</sup> It is absurd to believe with some interpreters of Galen that he really meant "soot." We are dealing here with one of those orthologic difficulties in that the Greek word which now means "soot" originally meant something entirely different and probably more in harmony with the opinions concerning the nature of venous blood of to-day.

[167] Michele Reves (better known by the anagram of Serveto or Servetus) published his book entitled, "Christianismi restitutio," which at the instance of Calvin resulted in the author's condemnation and death at the stake, in October of the same year, at Geneva. In this book about a theological matter (there are only two copies extant, since the greater number were burned, first at Vienne (Dauphiné) together with the effigy of the author, and then in Geneva simultaneously with the author<sup>o</sup>), there is a passage in which Serveto describes the lesser circulation, at the same time denying the communication of the two ventricles through the septum, and assuming that the blood from the right ventricle goes to the lungs where "flavus efficitur, et a vena arteriosa (arteria pulmonaris) in arteriam venosam (venæ pulmonales) transfunditur" (it is made brighter (yellow) and is transfused from the vena arteriosa (arteria pulmonis) into the arteriam venosam (venæ pulmonales)).

In the year 1559, that is to say six years later, Realdo Colombo, of Cremona, who for fifteen years had been prosector and then successor of Vesalius in the chair of anatomy at Padua, published at Venice his work entitled, "De re anatomica, libri XV," in which, on page 177, there is a description of the lesser circulation and a confirmation of the impermeability of the cardiac septum. The author lays great stress upon this discovery and claims the priority of it: "Nam sanguis per arteriosam venam ad pulmonem fertur, ibique attenuatur; deinde cum ære una per arteriam venalem ad sinistrum cordis ventriculum defertur; quod nemo hactenus aut animadvertit, aut scriptum reliquit." (For the blood is carried through the "*arteriosam venam*" to the lungs, and there it is attenuated, thence (mixed) with air, it is carried through the "*arteriam venalem*" to the left ventricle of the

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<sup>o</sup> Henri Tollin, l. c., presents convincing reasons for believing that numerous additional copies must have been in existence during Harvey's time of Servetus' "Christianismi restitutio" and that it would be incredible to assume that such an omnivorous reader like Harvey was not familiar with the physiologic contents of this book.

heart; which no one up to this time has either observed, or left [167] it in writing.)

It cannot be denied, that, if we consider solely the dates of the two publications the priority of the discovery belongs to Servetus, and if one could prove (as Tollin and Preyer in Germany and Willis in England have attempted to do) that Colombo had read the "*Christianismi restitutio*" of Servetus, then the Cremona anatomist would have to be declared guilty of plagiarism. But this is refuted by a number of incontrovertible facts, which G. Ceradini (1876-77) arranged with great acumen.

Ceradini emphasized that Valverde, a Spanish pupil of Colombo, in a text-book on anatomy published at Rome in the year 1556, ascribed the theory of the impermeability of the septum to his teacher. The book is preceded by an introduction dated 1554, in which the author states that he had already caused to be made numerous plates for the embellishment of his book, which must have taken at least a year. Thus we reach the year 1553, in which Servetus published the book which cost him his life. The assumption seems justified, therefore, that Colombo had already for some years taught his theory in his lectures before he published it in [168] his text-book.

It has been demonstrated that the passage in the "*Christianismi restitutio*" treating of physiology was only discovered towards the end of the seventeenth century. Ceradini further calls attention to the fact that in the year 1571 G. Günther, who, as professor of anatomy at Paris, had been the teacher of Servetus and Vesalius, in describing the lesser circulation in the words of Colombo, lauded the latter, without mentioning his own pupil Servetus, a proof that he did not know the "*Christianismi restitutio*." It is also probable that it was unknown in Italy, since it was not on the "*Index librorum prohibitorum*" edited by the Council of Trent and published at Rome under Pius IV in the year 1564, whereas this does contain two other heretical works of Servetus, "*De trinitatis erroribus*."

Finally Ceradini brought forward a splendid proof of the



[168] fact that Colombo had not plagiarized Servetus, in the comparison of the two theories.

Colombo denied the permeability of the cardiac septum completely and unconditionally; he emphasized the fact that not only the vena arteriosa, but also the arteria venosa was of considerable size; he further denied—even if incorrectly—the Galenian function of breathing, that is to say the formation of “soot” in the blood and the expulsion of the same by exhalation. Servetus on the other hand denied to be sure the existence of openings in the septum, but admitted that through it “aliquid resudare possit” (something could be expelled), and upheld the Galenian theory by the assumption that the blood “in ipsa arteria venosa inspirato aëre miscetur, et expiratione a fuligine expurgatur” (in the arteria venosa itself is mixed with inspired air, and is cleansed by expiration from the “soot”).

This question is a family quarrel among the Italian and Spanish anatomists and physiologists themselves, hence the sentiment due to national bias cannot be excluded in the conclusion of Luciani (professor of physiology at Rome), who says: “We will not go so far as to consider the hypothesis of Ceradini proved, that Servetus took the theory of the lesser circulation from Colombo, and tried to harmonize it with the old theory of Galen; but there can hardly be any doubt that the Cremona anatomist (Colombo) taught his theory for some time before it was published by the Spanish physician and theologian (Servetus).”

It is also of interest to determine to what extent Vesalius of Brussels was concerned in this theory, the great founder of modern anatomy, to whom Flourens (1857) ascribed the priority of the theory of the impermeability of the septum, while Henri Tollin (1884) accused him of plagiarizing Servetus, in which opinion Tigerstedt (1893) concurred.

In a recent publication<sup>7</sup> von Tackschath asserts that Vesalius is guilty of “plagiarism” and to have taken his anatomy—the “*Fabrica*” (1543) from Leonardo da Vinci.<sup>8</sup>

<sup>7</sup> Wien. med. Blätter, No. 46, 1902.

<sup>8</sup> See also Münchener med. Wochenschr., Mai 3, 1904, p. 821.

In the first edition of his great work, "De humani corporis [168] fabrica" (1543), Vesalius says that he is forced to admire the art of the master, who through invisible pores caused the blood to penetrate from the right into the left ventricle. In the second edition of the same work, which appeared in 1555, this expression of admiration for the creator is lacking, and the author declares that he cannot understand how "per septi illius substantiam ex dextro ventriculo in sinistrum vel minimum quid sanguinis assumi possit" (he could assume any substance even any blood to pass through the septum out of the right ventricle into the left).<sup>9</sup>

This more correct point of view, according to Tollin, was obtained by Vesalius from the "Christianismi restitutio" which Servetus had published two years previously, in 1553. It seems likely that Vesalius was using irony or sarcasm in the above expression, for he later on admitted that "*he accommodated his statements to the dogmas of Galen.*"

But Ceradini proved convincingly, through a long series of quotations from the above work of Vesalius and also from some of his smaller publications, that Vesalius had become acquainted with the impermeability of the septum at Padua in the year 1543 through his prosector Colombo, and that he had defended it at Pisa in the year 1543, without however expressly emphasizing the necessary physiological consequence of this, that is to say the theory of the lesser circulation and the necessity, already recognized by Galen, of anastomoses between the arteria venosa and the vena arteriosa; he wished to avoid giving possible glory to Colombo, against whom he always had a grudge, because the latter had apparently sought to incite the students at Padua against him.<sup>10</sup>

In the "*Ergebnisse der Physiologie*," Jahrgang II (1903), Biophysik, R. Tigerstedt presents an article on the lesser circulation (p. 533) which begins with a chapter "Zur

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<sup>9</sup> For fuller English translation, see Sir Michael Foster, Lect. Hist. Physiol., p. 14.

<sup>10</sup> See Michael Foster, l. c., and Henri Tollin, Colombo's Antheil an der Entdeckung d. Blutkreislaufs. Virch. Arch., Bd. 91, 1883.

- [168] *Geschichte des kleinen Kreislaufs.* Tigerstedt here accepts the opinion of M. Roth ("Andreas Vesalius Bruxellensis, 1514-1564, Berlin") that the lesser circulation was discovered by Colombo. The doubt which is thrown upon the anatomical knowledge of Servetus in this article is by no means substantiated by the contemporary literature, nor by the impressions gained from the writings of Servetus themselves. Tigerstedt, following M. Roth, asserts that Servetus does not present real but speculative anatomy—that his main desire is to bring about an accordance between the Bible and anatomy by compilation from preëxisting books, not from actual dissections. He denies that the recognition of the impermeability of the septum was original with Servetus, but ascribes this to Vesalius, a credit, which, as can be demonstrated from Vesalius' own "*Fabrica*," etc., stands on very feeble evidence. For it is on this point, "the impermeability of the septum," on which every student of anatomy must regret the uncertain language of Vesalius. Servetus, who had been prosector for Günter (Günterius), professor of anatomy at Paris (Tollin), cannot be accused of having learnt his anatomy from books alone.
- [169]

Without therefore trying to belittle the great services of Vesalius in the reformation of anatomy, one can nevertheless regard it as an established fact that he had no direct share in the discovery of the circulation of the blood. Indirectly, however, he aided in this by his refutation of numerous errors of Galen, especially the theory of the formation of blood by the liver. The fact that the lumen of the vena cava in the neighborhood of the heart is greater than at the liver, was for him a sufficient reason to return to Aristotle's theory of the formation of the blood by the heart, and to assume that not only the arteries but also the veins are offshoots from the heart.

In 1543 Vesalius was called by Cosimo I of Medici to become a professor at Pisa, where he determined to give a course in "*amministrationes anatomicæ*" on the errors of Galen. It is probable that among his auditors was numbered Andrea Cesalpino of Arezzo, at that time scarcely nineteen years of age, to whom belongs the fame of being the first to

have recognized and demonstrated the general circulation of [169] the blood.

In the year 1571 the physician and philosopher of Arezzo published his "*Peripateticarum questionum libri quinque*," in which he assumes, that in all parts of the body there is physiologically a constant transition of blood from the arteries to the veins by means of anastomoses, which he defines as "*vasa in capillamenta resoluta*"; the constant motion of the blood from the veins to the right side of the heart, from this to the lungs, from the lungs to the left side of the heart, and thence into the arteries he defines as "*Circulatio*." He was the first to recognize the arterial structure of the pulsating vessel which arises at the right ventricle, and which Galen had designated as "*vena arteriosa*," and the venous structure of the non-pulsating vein which was formerly designated as *arteria venosa*. He recognized further that the blood in the arteries is under a much higher pressure than in the veins, and that at its transition from the former to the latter the capillary anastomoses offer a greater or less resistance according to the degree of their contraction or expansion.

Twelve years after the "*Quæstiones peripateticæ*" appeared his books "*De plantis*" which alone would suffice to win for him imperishable renown as the forerunner of Linnaeus. In this work also he confirms that "*sanguinem pervenas duci ad cor, et per arterias in universum corpus distribui*" (that the blood is led through the veins to the heart, and is distributed by the arteries to the entire body).

In the year 1593 appeared Cesalpinus' work "*Quæstionum medicarum libri II*," in which he gave the experimental proofs of his theory. He observed that if in a living animal a vein is exposed and tied, and if soon thereafter an incision into the vein is made in the direction of the capillary, that the blood first appearing has a darker color, and that which flows out subsequently is lighter in appearance. From this observation he, with great acumen, deduced the physiological purpose of the anastomoses found in all organs between arteries and veins, in that he assumed: "*venas cum arteriis adeo copulari osculis ut, vena secta, primum exeat sanguis venalis*



169] nigrior, deinde succedat arterialis flavior, ut plerumque contingit" (that the veins are so connected with the arterial mouths that the vein being divided, first exudes a darker venous blood, then succeeds the brighter arterial, so for the most part it happens).

A second experimental proof of the circulation he founded upon the fact that in any part of the body the tied veins swell between the ligature and the capillary origin, and not between the heart and the ligature, as ought to be the case according to Galen's conception: "intercepto enim meatu, non ultra datur progressus; tumor igitur venarum citra vinculum debisset fieri" (for the course being blocked, no longer a flow is permitted; therefore the swelling of the veins ought to be made on this side of the ligatures) (*i. e.* between vein and capillaries)).

In spite of these brilliant experimental proofs of the theory of circulation, which Cesalpinus was the first to offer, the view was held by some, and among them the famous Haller, that he had indeed known the circulation of the blood but had only assumed it for the state of sleep, not during the awake state; they based their view upon a quite erroneous construction of a passage in which Cesalpinus assumes a certain reflux of the blood from the arteries towards the heart during the state of being awake. No one has better, and with more cogent logic, reduced *ad absurdum* the assertion of Haller than has Ceradini. It is a pity that Ch. Richet in his "Dictionnaire de Physiologie," which is now in progress, repeats the erroneous opinions of Haller concerning Cesalpinus, which had already been refuted through the historical-critical studies of Ceradini; which Ch. Richet certainly cannot have taken into account. (Luciani, l. c.)

H. Tollin, in a very thorough study of the life and work of Cesalpinus, concedes that this philosopher knew the greater circulation ("hat den grossen Kreislauf gekannt") but did not comprehend it.

A further very convincing proof of the circulation of the blood is found in the presence of the little valves, which are found in great number in the course of the veins, and which

are so arranged that they only permit a centripetal flow of the [169] blood and prevent a centrifugal flow. These valves Aquapendente knew and described, but did not comprehend their object.

This proof Cesalpinus did not take into account, with which fact Sprengel, a historian of medicine, reproaches him. It is a fact, however, that although Cannano of Ferrara as early as 1547 described a few of the valves of the vena azygos, and determined that their concave side was turned toward the heart, and although a few years later Fabricius of Aquapendente had found analogous valves in the entire venous system, and had demonstrated them to his pupils, he published his discovery "De venarum ostiolis" only in 1603, that is ten years after the appearance of Cesalpinus' "Quæstiones peri- [170] patecicæ."

On the other hand it must be stated that Fabricius, the describer of the valves in the entire venous system, did not recognize at all the function of the same, which consists in preventing the reflux of the blood in a centrifugal direction and to aid the centripetal flow during muscular activity; he thought on the contrary, that they were intended to retard the flow of the blood from the heart to the periphery of the veins. Who then was the first to base the theory of the circulation of the blood upon the function of the venous valves?

To Ceradini is due the credit of having brought to light a series of important documents which lead to the conclusion that the first to recognize the function of the venous valves was the famous theologian and canonist of the republic of Venice, Paolo Sarpi, the friend and pupil of Fabricius. It is a fact that some contemporary authors ascribed to Sarpi the discovery of the circulation of the blood. Brother Micanzio, Bartholin, Vesling, Gassendi, and Walaeus name him as the discoverer. Voss (1685) wrote that the discovery made in Italy by Cesalpinus of the circulation of the blood "Paulo Sarpi veneto in primis placuit." Vesling wrote to Bartholin that he had seen in the possession of Brother Micanzio after the death of Sarpi an autograph of the latter, *in which the*

[170] *circulation of the blood was described.* The famous Dutch physician Walaeus wrote in the year 1640: "Paulus Servita Venetus valvularum in venis fabricam observavit accuratius . . . . ex valvularum constitutione aliisque experimentis, sanguinis motum deduxit egregioque scripto asseruit" (observed more accurately the device of the valves in the veins . . . . from experiments on the construction of the valves he deduced the movement of the blood, and defended it in an illustrious writing (thesis)). Unfortunately, however, the manuscripts of Sarpi which were preserved in the library of the Servitians at Venice were destroyed, together with a large portion of the monastery, by a fire in September, 1769, and there was preserved only a passage cited from a letter, in Grisellini's book entitled, "Del genio di fra Paolo Sarpi" (Venice, 1783), in which letter Sarpi makes allusion to that which he "had observed and written down concerning the circulation of the blood in the vessels of the animal body and the structure and function of the venous valves."

What credit then belongs to William Harvey, the British discoverer of the circulation of the blood, after Servetus and Colombo, after Cesalpinus, and Sarpi? Certainly he was not the first to correct the error of Galen relative to the permeability of the septum and to assume that all the blood passes from the right side of the heart through the pulmonary vessels into the left side: this was the discovery of Colombo and Servetus. It was not he who first recognized the presence of arterio-venous anastomoses, the passage of the blood through the same and the centripetal direction of the course of the blood in the veins: this was the great discovery of Cesalpinus. It was not he, who first described the venous valves, for already Cannano knew of them and his teacher Fabricius d'Acquapendente described them in detail—it was not he who discovered the physiological importance of the same for the circulation; this was probably the discovery of Paolo Sarpi. And yet great credit is due to Harvey, for the reason that he more clearly defined the theories of his predecessors, and firmly established them by numerous vivisections and ingenious ex-

periments. The modern Italian physiologists (Luciani,<sup>11</sup> l. c.) [1701] accuse him of having committed a great wrong by trying to claim the glory of the discovery, not mentioning the names of Cesalpinus and Servetus, and making it appear that he did not know of their works.

After the historical-critical studies of Ceradini and also those of Tollin (which agree in this point) it would be absurd to assume that Harvey was not fully acquainted with the works of Cesalpinus, which appeared at Venice in the year 1593, that is, five years before Harvey took up his abode at Padua, where he remained four years (1598-1602) as the pupil of Fabricius d'Acquapendente. If he remained silent in the face of the charges of his contemporaries Micanzio, Vesling, Walaeus, Riolan, Bartholin, and others, who accused him of plagiarism, it was evidently because he wisely wished to refrain from entering into a discussion in which he had much to lose and nothing to gain.

In spite of all this his pamphlet of 72 pages, which appeared at Frankfurt in the year 1628, "*Exercitatio anatomica de motu cordis et sanguinis in animalibus*" is without doubt the masterpiece of a man of genius.

Even at the present day, after the lapse of more than two and one-half centuries of scientific investigation, this "*opusculum aureum*," as Haller called it, calls forth admiration of the reader, by the clearness of his ideas, and the logical arrangement of the observations, all of which were based on vivisection. With the exception of a few inaccuracies and errors, everything in the book is well observed and well conceived, and it can still at the present day serve as an introduction into a more detailed study of this interesting subject.

Upon laying bare the cardiac region of living animals, he observed that the heart is alternately in motion and at rest. During systole it rises, and with its apex moves the parietes of the chest; it contracts in its entirety, and especially in its lateral portions; it becomes hard, like the muscles of the arm

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<sup>11</sup> See Luigi Luciani, *Physiologia*, Vol. I, p. 125, translated into German from the Italian by Silvestro Baglioni, Winterstein, 1904.



[170] when they contract, and in the case of the cold-blooded animals it grows pale, because all the blood is sent out from its cavity. Pulse of the arteries is synchronous with systole of the heart. When the heart is at rest, the arteries also cease pulsating. If one open an artery, the blood gushes forth violently at each systole. Accordingly, at the moment of systole the blood is driven into the arteries, and cannot flow back, because the cardiac valves prevent reflux.

Like the ventricles, so also the auricles contract and relax, but earlier than the ventricles. The motion seems to start from the atria, proceeding thence to the ventricles. When the [171] heart dies, the left ventricle is the first to stop, then follows the left auricle, then the right ventricle, and the "ultimum moriens" as already Galen had observed, is the right auricle. If one cut through the apex of the heart at a moment when only the right auricle continues to contract, one sees blood coming forth at each contraction. Therefore the blood is driven into the ventricles by the contraction of the auricles, and not through the suction produced by the expansion of the ventricles.

The function of the motion of the heart is to force the blood coming from the veins into the arteries and thus distribute it over the entire body. Since the interventricular septum is impermeable, all of the blood, as has been recognized by Colombo, must go by way of the vena arteriosa and the arteria venosa through the lungs in order to pass from the right into the left ventricle. In all of this there is nothing essentially new, only the correction of some errors of Galen relative to the motion of the heart.

The conception of the general circulation is clearly expressed by Harvey in the following words: ". . . . patet sanguinem in quodcumque membrum per arterias ingredi, et per venas remeare; et arterias vasa esse deferentia sanguinem a corde, et venas vasa et vias esse regrediendi sanguinis ad cor ipsum; et in membris et extremitatibus sanguinem (vel per anastomosin immediatam vel mediate per carnis porositates, vel utroque modo) transire ab arteriis in venas; sicut ante in corde et thorace a venis in arterias: unde in circuitum

moveri, illinc hue et hinc illuc, e centro in extrema scilicet, et [171] ab extremis rursus ad centrum, manifestum fit" (it is evident, that the blood enters every portion of the body through the arteries, and returns through the veins; and that the arteries are the vessels carrying the blood *from* the heart and the veins are the vessels and ways of returning the blood to the heart again; and that in the members and extremities the blood passes from the arteries into the veins (either by *immediate anastomosis*, or mediately through *porosities* of the flesh, or by some other way?); as before was made manifest, in the heart and thorax from the veins into the arteries; thence to move in a circuit, now in one direction, now in the reverse, manifestly from the center to the extremities, and from the extremities back to the center.) From his own words we recognize that Harvey evidently was ignorant of the capillaries.

To prove his assertions, he furnished experimental proof of the three following theses:

1. The blood propelled by the contraction of the heart passes incessantly from the vena cava into the arteries, in such quantities, "ut ab assumptis suppeditari non possit, et adeo ut tota massa brevi tempore illinc pertranseat" (that it could not be furnished by the food consumed, and in a measure that the entire mass will flow through thence in a brief time).

2. The blood propelled by the pulsations of the arteries penetrates incessantly into every member or every part of the body, "majori copia multo, quam nutritioni necessarium sit, vel tota massa suppeditari possit" (in far greater abundance than is necessary for nutrition, even if the whole mass (of the body) could be supplied).

3. Ab uno quoque membro ipsas venas hunc sanguinem perpetuo retroducere ad cordis locum" (from any member its veins perpetually carry back the blood to the heart).

The demonstration of the first thesis is the most substantial portion of Harvey's work. Starting with the capacity of the right ventricle in human corpses (which is slightly more than three ounces of blood), he emphasizes the fact that a considerable quantity of blood must be driven into the arteries at

[171] each systole, in consequence of the size of the orifices (?) and the force of the contraction. However large this quantity be, it must be in proportion to the difference between the capacity of the contracted and the dilated ventricle. If the heart of man or of other animals convey only a single dram of blood at each contraction, and if in half an hour it perform a thousand contractions, the result is, that the heart in this short space has driven ten pounds and five ounces of blood into the arteries, a quantity which is much too large to be supplied by the food taken into the body, unless the blood return in the same way. One need not open the aorta, but merely any small artery, in order to cause all the blood of the body to gush forth in less than half an hour, as Galen already observed.

The demonstration of the second thesis is only an expansion of the experiments and ideas of Cesalpinus. If one apply a tight ligature to an arm, as in the case of amputations, pulsation of the arteries ceases in the periphery, while the arteries toward the center beat more violently and swell. The hand and arm cool after some time. If the ligature be only loose, as in the case of blood-letting, then the arm swells below the ligature, and the expanded veins appear prominently. Above the ligature on the contrary they become invisible. By the tight ligature the passage of the blood through the arteries is prevented, while the loose ligature prevents the course of the blood in the veins. Therefore the blood passes from the arteries into the veins. Here Harvey, with only slight changes, repeats the final deduction of Cesalpinus: "*. . . . apparet qua de causa in phlebotomia . . . . supra sectionem ligamus, non infra*" ("from which cause it is manifest that in phlebotomy we bandage above the cut and not below").

Also the conclusion drawn from this, that the blood flows toward the various organs in much larger quantities, "*quam nutritioni sufficiens sit*" ("than is sufficient for nutrition"), is taken from Cesalpinus, who designated as "*alimentum nutritivum*" that which the blood carries along for the nourishment of the organs, and as "*alimentum auctivum*" (growing) the part which returns to the right side of the heart, after

passing from the arteries through the capillaries into the [171] veins.

The proof of the third thesis is founded entirely upon the physiological function of the venous valves. Harvey treats this point with great acuteness, since it is best adapted to convince the incredulous, and he adds four illustrations of ligatured arms (one of them being simply a reproduction of "*Figura I, Tabulæ II, brachii vivi ad sanguinis missionem ligati*" (living arms ligated to hinder the flow of the blood) [172] from the treatise of his teacher Fabrizio (Fabricius ab Aquapendente), "*De venarum ostiolis*," which exhibit the veins swelled varicosely at the place of the valves. The venous valves do not serve the purpose of preventing a superfluity of blood in the lower portions of the body, for they occur also in the *venæ jugulares*, which go from above down, similarly in the *venæ emulgentes*, *mesentericæ*, etc. They serve rather to prevent a rushing of the blood from the larger into the smaller veins, so that the latter may not tear and become varicose, they prove that the blood in the veins does not flow from the center to the extremities, but from the latter to the center. Injections through the larger into the smaller veins are often arrested by the resistance of the valves, while in the case of injections through the small into the large veins there is no obstacle.

If on the ligatured arm one press the blood out of a vein with the finger, one sees that when the blood arrives above a nodule (which shows the position of a valve) (nodule) it cannot flow back again, and the portion of the vein between the nodule and the finger appears obliterated.<sup>12</sup> Accordingly the function of the venous valves is the same as that of the semilunar valves of the aorta and the *vena arteriosa* (*arteria pulmonaris*), which close the orifice and prevent a reflux of the blood.

One would think that the theory of the circulation of the blood, which had already been demonstrated by Cesalpinus, would, through its perfection at the hands of Harvey, have

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<sup>12</sup> See Figs. 1 and 2, above.



[172] immediately been accorded scientific citizenship, and be recognized by all. But opponents were not lacking, and among the most important and at the same time most persistent of them was Jean Riolan (Riolanus), a famous Parisian anatomist, and Kaspar Hoffmann, a leader of German science of that period, who had been, like Harvey, a pupil of Fabricius d'Aquapendente at Padua. They recognized, indeed, that the new doctrine would result in the total collapse of the system of medicine

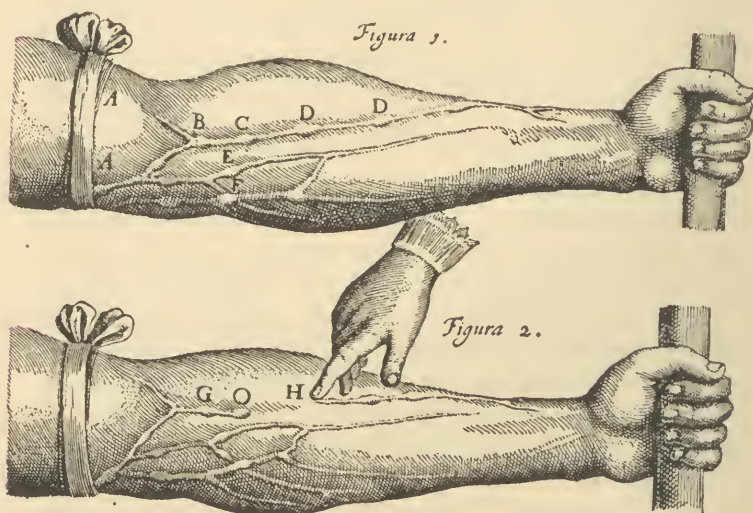


Fig. 1 is a reproduction (Photozinkography) of the two first figures of Harvey's work, edition 1639, ex officina Joannis Maire, Lugduni Batavorum.

Fig. 1 is an exact imitation of the illustration in Fabrizio's writing "De venarum ostiolis." At AA the arm is ligated as is customary in venesection. One sees the swollen veins, which show enlargements at the points B, C, D, E, F, which proceed from the valves. These are not only found at the bifurcations (E, F), but also at (C, D).

Fig. 2 shows the same arm in which the blood has been forced from O to H, by drawing the finger forcibly along it from H to O. The portion of vein H to O appears to be obliterated, because a valve exists at O, which prevents the blood from flowing back to H, and the finger pressing upon the vein at H prevents the blood from flowing in from the peripheral veins.

of the period, and every means seemed justified in preventing this, which in their eyes at least seemed a deep disgrace. It is scarcely necessary to say that this opposition (although it disclosed some mistakes and errors of Harvey's work) only aided in propagating and advancing the new theory. And thus the remark of Ceradini seems very apt, that "Harvey owed his success to the opposition of the Parisian anatomist, who, upon Fabricius' death was considered the greatest authority in Europe; and the error of the partisans of the Englishman arises from the parallel which they drew from the impression which his writings made in the scientific world, as compared with those of Cesalpinus. . . . Had Cesalpinus during his life met with a Riolan, to accuse him of plagiarism, absurdity, and of heresy, the very slow development of his ideas concerning the circulation, in lectures covering a period of more than thirty years (first at Pisa then at Rome), would have been impossible without discovering the possible results and applications of the same, no one could have taken from him the great renown of his discovery."<sup>13</sup> Furthermore, Harvey himself was at the beginning so far from having any idea of the far-reaching consequences of the doctrine of the circulation of the blood, which he had learned from Andrea Cesalpinus, that he only thought of printing it after he had for nine years treated of it in his lectures; he was only impelled to do so by the fact that this doctrine had made both friends and enemies for him, and that the latter made a great stir about it. And even after the appearance of his book, in the year 1649, the physiological importance of the theory seemed to him so problematical, that in his answer to Riolan, who declined to accept the theory, because he could see "*neque efficientem, neque finalem causam*" (neither the influence, nor the final effect) he had no better reply to make than to say: "*Prius in confesso esse debet quod sit, antequam propter quid inquirendum. . . . Quot sunt in physiologia pathologia*

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<sup>13</sup> Ceradini here means that the complete comprehension of a discovery is often not made by the discoverer himself, but he may be brought to a wider comprehension of his contributions to science by the opposition of men of authority.

- [172] et therapeia recepta, quorum causas non novimus, esse tamen nullus dubitat?" (first it ought to be conceded what may exist, before inquiring what it means or wherefor. . . . How
- [173] many things there are received in physiology, pathology and therapeutics, whose causes we know not, yet no one doubts their existence?)

As long as the theory of Aristotle flourished, which had been rehabilitated by Cesalpinus and Harvey, that the function of the lungs consisted in refreshing the blood, and that this organ, in which the blood was again made spirituous and thin was nourished by the thick blood flowing back from all the organs; as long as especially the place of blood-formation remained unknown, and also the channels through which the products of digestion reached the circulatory system; just so long did the theory of the circulation of the blood remain without its true significance, and it could only be regarded as a physiological curiosity.

To judge from certain passages in Galen, it seems as if Herophilus and Erasistratus, the heads of the Alexandrian school (300 B. C) had seen the chyloferous vessels in the mesentery of the sheep. Towards the end of the 18th century Portal remarked, as in fact also Fracassatus had done more than a century earlier, that the celebrated Roman anatomist Eustachius,<sup>14</sup> in studying the course of the *vena azygos* in the horse, had observed the thoracic duct and even some of the valves of the same. But it is certain that every trace of these accidental and isolated observations had vanished to a vague tradition, when Gaspare Aselli of Cremona, professor of anatomy at Pavia, found, in 1622, the chyloferous vessels in the mesentery of the dog, designating them by the name of lactiferous vessels. So happy was he at having found what he had been seeking, that, as he relates, "*conversus ad eos qui aderant: εὐρηκα, inquam cum Archimede*" ("I turned to those who were present: I exclaim with Archimedes, Eureka"). But as yet he had no idea of the true function and physiological importance of these vessels.

In the year 1648 Pecquet, a young physician of Dieppe, who

<sup>14</sup> *Opuscula anatomica, Venetiis, 1564.*

was studying in Montpellier, found that the lactiferous vessels do not send their contents to the liver, as Aselli had believed, but to a large vessel, the thoracic duct (re-discovered by him after Eustachius) which empties into the subclavian vein. Two years later Rudbeck, a Swede, discovered the lymphatic vessels of the liver, and recognized that they also send their contents to the thoracic duct. Finally, in the year 1652, the famous Danish anatomist, Thomas Bartholin, discovered the same vessels in all parts of the body, and found that all of them, together with the chyloferous vessels, flow into the thoracic duct. In order to give further scope to the theory of the circulation of the blood, ascribed by him to Harvey, he published a new edition of his anatomy "*ad sanguinis circulationem reformata*," being correctly convinced that he had furnished a new argument in favor of it, indirect to be sure, but nevertheless valuable.

According to Ceradini, "Riolan himself, the upholder of every old doctrine, and the opponent of everything new, in this case withheld the sharp arrows of his criticism, in order not to see them rebound harmlessly from the strength of facts. Harvey, however, DENIED THE EXISTENCE OF THE CHYLIFEROUS and LYMPHATIC VESSELS, and EVEN THE FUNCTION OF THE THORACIC DUCT, and died without being converted, in the year 1658, six years after the death of Bartholin. Luciani (professor of physiology in Rome), in his elaborate handbook on human physiology, expresses surprise and regret that Sprengel, the famous historian of medicine, scarcely mentions this "*ugly trait in the character of the Englishman, this contempt for every discovery which was not his own, a blemish which would be inexcusable, even if Cesalpinus had not demonstrated the circulation of the blood before him.*"

In order to complete the new theory, and to bring it to a state of absolute certainty, there was now only lacking the last decisive step, the discovery of the capillaries of the blood and the direct observation of the circulation of the blood through these capillaries from the arteries to the veins. "Supererat" (it remains), as Haller said, "ut ipsis oculis cir-



[173] *cuitus sanguinis subjiceretur*” (that the circulation of the blood be subjected to the eyes (be actually seen)).

Galen, who, as already mentioned, was the first to assume direct communication of arterial and venous vessels in the organs, thought of a kind of direct anastomoses or a simple meeting of the two kinds of vessels. This was not in accord with the idea which Cesalpinus had formed; the latter conceived that the junction was made “*per vasa non desinentia, ulterius transmeantia*” (by vessels not stopping, but passing through), or “*per vasa in capillamenta resoluta*” (by vessels broken up into hairs (threads)) (which Harvey changed to “*per carnis porositates*”) (through porosities of the flesh), and Cesalpinus thus guessed the existence of a new kind of vessels, which unite the arteries with the veins and which then were called capillaries.

Marcello Malpighi, with the aid of the microscope, was the first to observe the motion of the blood in the capillaries of the lungs of the frog. This was in 1661. With just pride he exclaimed: “*Talia mihi videre contigit, ut non immerito illud Homeri usurpare possim ad rem præsentem melius; magnum certum opus oculis video*” (it has happened to me to see such things, that not undeserving I might in the present instance use the saying of Homer: I see with my eyes a sure great work).<sup>15</sup>

After Malpighi, vain attempts were made by Leeuwenhoek, Cooper, and Haller to extend these observations also to the warm-blooded animals. The first to succeed in this was Lazzaro Spallanzani, who hit upon the idea of making use of the hen's egg during the process of development of the chick. The enthusiastic words with which the great physiologist reports his discovery cannot but provoke a smile. “For a long time I had been burning with the desire to discover the circulation of the blood also in the case of the warm-blooded animals, to observe it in the same degree in which I had noticed it in cold-blooded animals, and thus these vessels (the *vasa umbilica* of the chick) attracted my attention more than

<sup>15</sup> Cf. Fig. 48.

anything else, because they belonged to that species of animal. [174] Since the room in which I was, did not have sufficient light and I was determined in some way to satisfy my curiosity, I resolved to examine the egg in the open air, by direct sunlight. After I had fastened it to the small Lyonet apparatus (a small microscope, used by Spallanzani) I immediately focused the lens upon it, and in spite of the flood of light which surrounded me, I could, by partly closing my eyes, distinctly see the blood circulate through the entire complex of the arterial and venous umbilical vessels. Overcome by this unexpected pleasure, I felt at liberty also now to cry out: 'I have found it, I have found it!' I made the discovery in May, 1771, and in the summer vacation of that year I took pains to develop it suitably."

These observations of Malpighi and Spallanzani, separated by a century, constitute two of the chief events in the history of medicine. The glory of the first direct observation of the circulation of the blood belongs undoubtedly to the Italian physicians. Modern scientists, with more perfect microscopes and more advanced technical skill, have only been able to perfect the description of the circulation of the blood as seen under the microscope.

In speaking of Servetus, Sir Michael Foster does not concede to him any marked influence on the development of anatomic thought of his day, and declines to regard him as a real link in the chain which leads from Galen to Harvey.<sup>10</sup> He would concede to the writings of Servetus only isolated bits of truth, floating along the stream of human thought, by the side of other truths, the outcome of the labors of other men. But though Sir Michael Foster speaks in the diminutive concerning the work of Servetus, he makes use of this very author's work to minimize the merit of another contributor to the history of the circulation, namely, Matheo Realdo Colombo; for he suggests that Colombo might have taken the idea of pulmonary circulation from Servetus, and his reason is that in 1546 Servetus sent to Curio in Padua a manuscript copy of his "Restitutio." "This Columbus may have seen.

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<sup>10</sup> Lectures on the History of Physiology, p. 24.

[174] Again, when the edition of the published 'Restitutio' was burnt in 1553, some few copies escaped. One of these may have found its way to Rome before Columbus had sent his work to the press." Tollin<sup>17</sup> and Preyer<sup>18</sup> have arranged the quotations from Colombo and Servetus concerning the lesser circulation side by side, suggesting that Columbus learned what he knew from Servetus.

Sir Michael Foster furthermore attempts to support his charge of the plagiarism of Columbus from Servetus by what he calls an "unabashed attempt to assert ownership of the discovery of the third ossicle of the ear, the stapes." According to Fallopius, the stapes was first described by Ingrassius of Palermo, a Sicilian, in 1548. This may be, as Foster states, a theft, but it is not absolutely proven, because at the present day, two physiologists or anatomists, in different countries, have been known to make and claim an identical discovery simultaneously.

The character of Colombo is represented as having been that of a "vain and ungrateful successor of Vesalius,"<sup>19</sup> and his standing, it is indicated, suffered by his fulsome adulation of Pope Pius IV, a pope whose character has met with much criticism.

From the standpoint of critical conservatism we cannot conceive that the charges of plagiarism and theft against Colombo have been satisfactorily proven. At least they would not be accepted as proven by a judicial mind. I have already given the proofs in the preceding on the authority of G. Ceradini,<sup>20</sup> which are incontrovertible facts, that Colombo could not possibly have plagiarized Servetus. His accurate descriptions of the pulmonary circulation may be the results of his own research and subjective analysis. Some doubt is thrown on Ceradini's conclusion by the incomparably precise historic researches by H. Tollin,<sup>21</sup> who does not consider that Colombo

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<sup>17</sup> Virchow's Archiv., Bd. 91, 1883.

<sup>18</sup> Samml. physiolog. Abhdl., 1876.

<sup>19</sup> Puschmann Handb. d. Geschichte d. Medicin, Bd. 11, p. 331.

<sup>20</sup> Loc. cit.

<sup>21</sup> Loc. cit.

is original, but simply has confirmed what Servetus described [174] before him.

Concerning the merits of Andreas Cesalpinus,<sup>22</sup> Foster<sup>23</sup> suggests that "they were not the outcome of patient research, or real study of the phenomena themselves, but may have been flung out in the spirit of controversy, as effective assaults upon the accepted doctrine of the times." In the preceding, however, I have given the evidence that we have no right to question, that the theories as announced by Cesalpinus were not the outcome of real study of the phenomena themselves.

A personal and systematic study of Cesalpinus' works undeniably gives the impression that he was a man of most vacillating character, of insufficient force of conviction even where there was every probability that his views were correct. But even his greatest opponent, Tauriel (of Montbéliard), has much to say in praise of his versatility and the inventive power as displayed in the "*Quæstiones peripateticæ*," and that these talents when coupled with "love of truth and piety" would justify us in expecting great and useful things of Cesalpinus." ("*Qua sua singulari facilitate poterat prodesse plurimum—res magnas et humanæ societati utilissimas præstare possunt.*")

It cannot lead to a just opinion of Cesalpinus, to merely glean here and there in his works; isolated patches of his writings must inevitably present a disconnected, illogical character, whereas in truth his argument is as homogeneous and consequential as that of Colombo—whom Harvey honors and quotes to the total exclusion of Cesalpinus.

It is very regrettable that the great Haller made an erroneous construction of a passage from Cesalpinus, in which a reversal of the present idea of the circulation was assumed to take place during the waking state (a certain amount of reflux of blood from the arteries to the heart during the waking state).<sup>24</sup> The forcible logic of Tollin<sup>25</sup> and of Ceradini have

<sup>22</sup> See preceding.

[174]

<sup>23</sup> Loc. cit., p. 35.

<sup>24</sup> See preceding.

[175]

<sup>25</sup> Loc. cit.



[175] set the views of Cesalpinus in the right light, and proven that he was a physiologic experimenter of ability. He had not only grasped clearly the pulmonary circulation, but also the systemic circulation. There is no doubt whatever that he knew that the flow of blood to the tissues took place by the arteries, and that the return of the blood from the tissues took place by the veins and not by the arteries. The published works of Colombo and Servetus to my mind represent independent and individual conceptions. The charges of plagiarism of one from the other, are ingenious speculations.

It cannot possibly deduct from the brilliancy of Harvey's genius to have the work of his predecessors set in the right light. His admirable combination of anatomical features with physiologic function, his conception of experiments, both original and conclusive, testing the validity of his explanations, all combine to complete the picture of a physiologic thinker of colossal ingenuity. If other workers preceding Harvey fell short of his results, it may of course have been due to a lesser intellectual endowment, but it may also have been due to the fact that they were working in countries in which scientific research was under the ban of Church and State. Furthermore, path-hewing is more difficult than path-widening. The older and preceding workers in any department of science do not, as a rule, grasp the entire truth concerning the relation of things. Scientific exploration takes place, as a rule, bit by bit, sometimes by strenuous and painful endeavor. The mental or subjective conceptions preceding the experiment being often more laborious than the actual devising of experiments to test the validity of the conception. All this in the discovery of the circulation of the blood took centuries.

As grateful recipients of the labors of the historic apostles of physiology, it behooves us to maintain a judicial mental attitude and interpret the contributions of each physiologic worker from the aspect of the condition and influences—political, religious, scientific, and otherwise,—that were predominating at his time, and in that light it is astounding to observe how near to the truth Servetus, Matheo Colombo, and Cesalpinus came with their crude methods of subjective and object-

ive analysis, and we will have to sum up in one abstract sentence with Professor L. Landois that "William Harvey, a pupil of Fabricius (until 1604) finally constructed, between the years 1616 and 1619, partly from his own investigations and partly from the results of former observers already mentioned, the picture of the circulation of the blood, the greatest physiologic achievement, which was published in 1628 and marks a new epoch in physiology." [175]

A RÉSUMÉ OF WHAT WE HAVE LEARNED FROM THE LITERATURE QUOTED IN THE PRECEDING ABOUT HARVEY AND HIS RELATION TO HIS PREDECESSORS.

We gather from Harvey's own writings and the scholarly studies of Henri Tollin,<sup>28</sup> that, seven years before his death, Harvey plainly teaches that before him there was a knowledge of the circulation of the blood. In "De Motu Cordis" and in his writings to Riolan he teaches that Realdo Colombo has shown that the blood does not pass from one ventricle into the other through the middle wall of the heart, but through a long circuit through the lungs. Harvey imparts to his friend Boyle that he got his first suggestion of a circulation of the blood from his Paduan teacher, Hieronymus Fabricius ab Aquapendente, led to the idea by meditation over the function of the valves in veins, and to his friend Ent, that Fra Paolo Sarpi (1623) had left a writing on the uninterrupted return of the blood (to the heart) five years before Harvey published his. Harvey declares it the duty of the scientific anatomist to learn the experiences of his predecessors, to prove and to use them. He abundantly makes use of this right and therefore walks in the foot-prints of Galen and Hippocrates, of Pliny and Aristotle, of Fernel and Vesalius, of Colombo and Aldrovandus, and of many, many other authorities. Harvey regards the moving blood as inseparable from the spirit, which first gives it movement, warmth, feeling, power of nutrition, even something heavenly, corresponding to "the element of the stars." Harvey makes this probable to us by many rela-

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<sup>28</sup> Loc. cit.

[175] tive thoughts, which he has drawn from not only Realdo Colombo, whom he cites several times, but also from Michael Servetus, Sarpi, and Andreas Cesalpinus. But through the proud, independent, indomitable peculiarity of his character, Harvey makes plain to us why, where the renown of a discoverer was at stake, he could not bring himself to say: "I am not the discoverer, but yonder Aristotle and Aquapendente, there Aselli, Pequet, Rudbeck, and Bartholin, there again Caspar Hoffmann, here finally Sarpi, Cesalpinus, Colombo, and already before them Michael Servetus."

I am well aware that Tollin's<sup>27</sup> conclusion may vary from the current, traditional jubilation over the great Harvey, the demonstrator of the entire circulation of the blood. But Tollin, if abused for this variation, will answer with the words of his teacher, William Harvey: "Trust in your own experiences, not in those of others" (*propria experientia nitendum est, non aliena* (Opp. 172)).

The completion of the discovery of the circulation of the blood by Malpighi and Leeuwenhoeck, by Eustachius, Aselli, Pequet, Rudbeck, and Bartholin, by the injections of Swammerdam, Horne, and Ruysch, the observation of invertebrate animals on the part of Willis and Milne-Edwards, by the discovery of graphic methods, by the observations of the vasomotor nerves on the part of Bernard, Brown-Séquard, Ludwig, lead Chapman<sup>28</sup> to the conclusion that "*the SPIRITUAL DEVELOPMENT of humanity is also a growth that is governed by life-laws, and that a discovery, although if it was not made by him to whose name it is wont to be attached, yet at the appointed time would have seen the light of the world.*" All circumstances show that towards the end of the sixteenth century intellectual Europe was ripe for the acceptance of the discovery of the circulation of the blood. If it had come a few centuries sooner, it would have died at its birth. Italy and particularly Padua were alive with speculations, hypotheses, and theories concerning the course of the blood through the body. One who will compare the Latin original of Harvey's

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[175] <sup>27</sup> Henri Tollin, *Arch. f. Pathol. Anat.*, Bd. XXXI, 81, Heft I.

<sup>28</sup> *Loc. cit.*

writing upon the circulation with the writings of the great [176] Italian anatomists and physiologists of the sixteenth century, will be astonished at the similarity of thought and expression. (The same mode of thought and expression pervade both.)<sup>20</sup> In the method of his investigation, observation, and conclusions, Harvey is essentially Italian. An Englishman by birth, an Italian in thought, Harvey lived and died as a student of Padua. Thus Chapman returns to where he started out. Between Galen and Servetus, the second and third epochs of the discovery, Chapman establishes an interval of 1718 years; between Servetus and Cesalpinus 40 years; between Cesalpinus and Harvey 35 years. When Servetus stood forth, he risked that his discovery might be burned with himself. When Harvey stood forth, all had been prepared. He came, considered, and gained the victory.

Tollin pointed out what an advance in the investigation of the history of the discovery of the circulation of the blood, even in Harvey's fatherland, since 1878 (the 300th anniversary of Harvey's birth), we have to record. Before 1878 it was not only the dogma of the profane crowd of the educated but also of the professionally educated in England, that as Minerva from the head of Jupiter, even so fully and entire, the discovery of the circulation of the blood sprang from the head of Harvey. Now even in England it is said: When Harvey came, everything was fully ripe. If he had not harvested, then at that time another would have come and gathered in the harvest. The seed sowing was the work of the Spaniards, especially of Michael Servetus; the watering, the care, the pruning the work of the Italians, especially of Colombo, Cesalpinus, Fabricius de Aquapendente. To Harvey remained the honorable, remunerative, although always troublesome work of the harvest. But what we possess to-day, we possess through him who harvested it for us. And for this Tollin designates the gifted Harvey, "the great Briton, the pattern of all harvesters and classifiers."

William Harvey, armed only with a magnifying glass, ac-

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<sup>20</sup> Tollin: Loc. cit.



[176] accomplished such great things that one cannot express what this genius would have accomplished had he, like Malpighi, been furnished with a microscope. But the discoverer of the blood circulation is not Harvey, however much, misled by the favor of two kings and the almost idolatrous reverence of his nation, he sought to convince himself that he was such. And he did convince himself and finally did believe in it, because this belief only too soon had become the dogma of his nation. But, in the moments when he is candid, he acknowledges that several persons before him, induced by Galen's authority and that of Colombo and Servetus, beside other reasons, had taught the truth about the blood-vessels and had expressed the opinion which he now claimed as his own; yes, that many, long before him, had known of a blood circulation, by means of which continually the blood passed from the arteries into the veins and from the veins returned to the heart; that he himself had gladly and diligently read the books of those who had borne the torch of truth before us, that he willingly paid due respect to those old authorities and only *had not mentioned particularly all of the modern ones in order not to give occasion for disputes*; and that it was he who had erected upon firm and necessary foundations, more distinctly, more orderly, and fully corresponding to the actuality, the blood circulation discovered before him.

We once more affirm Harvey, the author of "De motu cordis et sanguinis," 1628, did not discover the lesser circulation. This Servetus discovered in 1546. Harvey did not discover the greater circulation. This Cesalpinus discovered in 1569. Harvey did not discover the venal valves. These Jacob Silvius, Sarpi, and most accurately Aquapendente discovered in 1574. Harvey did not furnish the clear-sighted proofs of the circulation. These were given by Servetus, Colombo, Valverde, Aranzi, Ruini, Rudio, Sarpi, Cesalpinus, and Aquapendente. Harvey never saw the circulation of the blood. Malpighi saw it several years after Harvey's death (1661).

Strictly speaking, Harvey did not even describe the circulation, but a double half circulation. Whether in the lungs and in the extremities the arterial endings were in communi-

cation with the commencement of the veins by anastomosis, [176] or by infiltration of blood into the pores of the tissues, he never dared to decide, because the magnifying glass here failed to tell him. And so, since two half circulations suddenly end without a demonstrable continuation, there is no actual, no completed circulation.

Nevertheless, even then Harvey still remains an incomparable genius. For "*by the accuracy and thoroughness of his deductions, by the skillfulness, by the industry and the abundance of his experiments, by the carefulness and the delicacy of his observations, by the keenness and shrewdness of the proofs, by the clearness and truth of the conclusions drawn, by the novelty and importance of the interposed reflexions, above all by the harmonious connection of the whole,*" William Harvey, the great regius predemonstrator of the blood circulation, the movements of the heart and of the blood, has lifted these from a hypothesis of the darkest possibility to the clearest probability, from the recesses of single obscure studies to the shield of public opinion, from the individual views of a few favored ones to a dogma everywhere sanctioned. And in this sense one can indeed say with Tollin: "Without the school of Padua, yes without Erasistratus, Aristotle, Galen, Servetus, Vesalius, Colombo, Cesalpinus, Aquapendente, we would have had no Harvey, but without Harvey no discovery of the blood circulation."

Harvey quotes among the authorities known at and previous to his time Aristotle, Galen, Erasistratus, Vesalius, Realdo Colombo, and Fabricius de Aquapendente. He does not cite [177] Michael Servetus nor Cesalpinus, and yet he must have been acquainted with their works, for his methods of thinking show many resemblances to that of these writers. It is absurd to assume that such an omniverous reader as Harvey, who studied four years at Padua, where the works of these two men were widely known, was not acquainted with their writings. The omniverous reader, Harvey, who is described as accompanying King Charles I, and taking care of the princes, and during the battle of Edgehill (Oct. 23, 1642), as sitting at the outskirts

[177] of the fight under the hedge reading a book (Aubrey).<sup>80</sup> Furthermore, Robert Willis,<sup>81</sup> the greatest Harvey connoisseur in England, actually asserts that Harvey was a free-thinker like Servetus and Cesalpinus, and even an Antitrinitarian, so that he must have been in religious sympathy with these two men, and for this reason again he probably sought and was familiar with their works. And yet we will have to excuse him for not quoting these two early discoverers for the following reason:

Because of his heretic work "De Trinitatis Erroribus," Michael Servetus was burned at the stake at Geneva, in 1553.

Cesalpinus, free-thinker like Servetus, friend of Trismegistus and precursor of Spinoza, could only save his life by retracting.

Matteo Realdo Colombo was a diplomat, clerically inclined, friend of several cardinals and flatterer of the inquisitorially-minded pope Paul IV, his memory was held in high esteem at the English Court, whose queen was a devout Catholic, and whose king was secretly her ally. A hater of the Protestants, an enemy of all Puritans, and still more of the free-thinkers, a systematic adherent of a strict bishopric régime, the royal patron of Harvey was the man who sent the members of Parliament into prison, who made the method of punishment severe to the utmost to Anabaptists and Antitrinitarians, and applauded the massacre caused by Ireland's Catholics among the Protestants. As is well known, the king was beheaded in 1649.<sup>82</sup>

The Protestant England, with its independent spirit of inquiry, to whose free manner the Harvey jubilants attributed

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<sup>80</sup> Foster: Loc. cit., p. 42.

<sup>81</sup> Loc. cit.

<sup>82</sup> A court physician, under such a tyrannical prince, who would have dared to confess himself to Cesalpinus or even to Michael Servetus, would have certainly been executed, like Harvey's contemporary, the Saxon Chancellor Nicholaus Crell, who was beheaded for heresy at Dresden, the 23d of October, 1591, after ten years of imprisonment in a fortress. And Crell was not even a free-thinker, but a Protestant, who had the courage to prefer to be called a Christian, instead of a Lutheran or a Calvinist.

Harvey's great discoveries, did not exist at his time, and not [1771] for a long time after it. Harvey died the 3d of June, 1658. And still King Charles II, son of the executed Charles the first, forced on Bartholomew's Day, by his Acts of Uniformity, two thousand English clergymen to resign their positions because they refused to subscribe to the thirty-nine articles of the King's faith. Even quiet prayer-meetings in the attics were considered treasonable. The heretics were banished. None of the exiles were allowed ever to come again within five English miles of their villages or any English cities.

Twelve years after Harvey's death the nonconformist act was rendered still more severe. Indeed twenty years after his death nobody could venture to adhere publicly to Cesalpinus and Michael Servetus. Up to 1828 the Acts of Uniformity of Charles II governed, which excluded all nonconformists from Parliament and civil service, also from the office of a royal court physician, which meant so much for Harvey. Under the son of Harvey's patron, 80,000 Englishmen had to suffer all kinds of persecution because they refused to take oath to the faith of the State. Eight thousand alone had to go to prison for their faith.

James II, successor of Charles II, declared himself openly a Catholic, to destroy the last remains of the free faith by strict government without Parliament.

But his son-in-law, William of Orange, thirty years after Harvey's death, set up the famous Acts of Toleration in 1689. But free-thinkers, like Peter Bayle, were dismissed from their offices (1693) and those who sided with Servetus, called the Socinians, were expressly excluded from every public tolerance.

There are some who lauded Harvey's character up to the skies, just as they called (according to the legend) Harvey's mother the best of all women, probably because one knows nothing of her. But has nobody discovered a predestination as a martyr in a man who always kept his faith as secret as possible, and who deserted his royal benefactor as soon as the luck left the king's banners. No wonder, therefore, that Harvey does not mention Cesalpinus and Michael Servetus, even had he known them by heart.



[177] The fruit of an intellectual deed is frequently more evidenced in the incentive which that deed gives to investigation than in the actual contribution to science made therein. An immense industry was developed by the exact proofs of the circulation furnished by Harvey, diseases were conceived of in a new light, efforts at transfusion were made, and of injection of remedies into the circulation.

The discovery of the circulation of the blood was the work of almost a millennium from Aristotle and Galen to Harvey, but the one who first logically drew true consequences out of hundreds of years of preceding work, and upon whose broad intellectual shoulders all subsequent investigations rested, was William Harvey; and to-day, 328 years after his birth, we may side without reservation with the words of Bartholin: "At Harveyo omnes applaudunt circulationis auctori!"

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**Are the proteolytic and milk coagulating effects  
of gastric and pancreatic juice due to one and  
the same enzyme?**

By

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(Sonderabdruck aus der Berliner klin. Wochenschr., 1905, No. 44 a.)

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## **Are the proteolytic and milk coagulating effects of gastric and pancreatic juice due to one and the same enzyme?**

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The distinguished St. Petersburg physiologist, J. P. Pawlow, associated with S. W. Parastschuk, has published a series of experimental investigations under above heading in Hoppe-Seyler's Zeitschr. f. physiol. Chemie, Bd. 4, p. 315 to 452. (The exact title of the article is „Ueber die ein und demselben Eiweissfermente zukommende proteolytische und milchkoagulierende Wirkung verschiedener Verdauungssäfte.“) The view hitherto held and still held by most physiologists is that the proteolytic and milk coagulating effects of gastric juice (of pancreatic juice also), are due to specific enzymes. The earlier investigations on the subject date from Hammarsten (Maly's Jahresberichte, 1872, Bd. II, S. 118; see also Hammarsten's Lehrbuch der physiol. Chemie, 5th edition). In order to precisely state the direction of the inquiry it is necessary to emphasize that Pawlow and Parastschuk attempt to prove that a separate and distinct milk curdling enzyme does not exist, but that milk coagulation is only a property of the pepsin. The „Fragestellung“ here is not as precise as might be desirable, for proteolytic and milk coagulating effects might be conceived as attributable to one and the same proteid ferment, and yet pepsin and chymozin may be two different enzymatic effects, for we may conceive that pepsin, the proteolytic enzyme, possesses also to a certain extent a milk coagulating effect, which is only developed in an acid reaction and not in a neutral reaction, and as far as human



gastric juices are concerned, it can be stated that such an enzyme occurs which will curdle milk in the presence of an amount of HCl which, as a rule, is normal to human gastric juice (2 parts per thousand), but will not curdle milk if the gastric juice is exactly neutralized. This disappearance of milk coagulating power in the case of canine gastric juice, after it has been neutralized with sodium bicarbonate, was noticed by Pawlow and Parastschuk (l. c., p. 422), but they attributed this disappearance to a destructive effect of the alkalies employed, particularly to  $\text{Na}_2\text{CO}_3$ . When the juice was neutralized with  $\text{NaHCO}_3$ , the ferment could be preserved. To the destruction of the pepsin by alkalies they attribute their inability to separate these two enzymes by Hammarsten's method (shaking of gastric juice with magnesium carbonate, by which the pepsin is torn down by this insoluble powder, whilst the chymozin [Lab] remains in solution.) The third, fourth and fifth filtrates prepared in this way will coagulate milk energetically, but will not digest raw fibrin in 24 hours not even if raised to the normal acidity. But Pawlow asserts that when this filtrate was diluted 5 to 10 times its volume with XX 0,1 to 0,2 per cent solution of HCl, the proteolytic effect on fibrin became distinctly evident.

The two enzymes, however, can be separated in a much simpler manner — by heating gastric juice to  $65^\circ \text{C}$ . for ten minutes, the chymozin can be destroyed. When chymozin is in solution together with HCl — 3 parts per 1000 — the enzyme can be destroyed completely if the solution be kept at a temperature of  $37$  to  $40$  degrees C. for 48 hours (Hammarsten, l. c., p. 291). The pepsin is not destroyed by this process. In this manner a pepsin solution free from chymosin can be obtained. A solution of parachymosin, free from pepsin, can also be prepared in a similar manner (Ivar Bang, Ueber Parachymozin, ein neues Labferment, Pflüger's Archiv, Bd. 79, S. 425). Bang's investigations have made it very highly probable that the chymosin enzyme of different animals are by no means identical, but show striking differences in milk coagulating power. Accordingly it becomes necessary in testing the results of previous investigators, to use the chymosin from the same animals as they employed.

In „Beiträge zur chemischen Physiologie und Pathologie“, Bd. VI, H. 8, S. 396, P. Schrumph described a new method for preparing pepsin from the expressed juice of mucosa of pigs stomachs. Schrumph prepares four different solutions according

to the different chemical treatment to which he subjects this pressed juice of gastric mucosa. Solution **A**: minced gastric mucosa is thoroughly cleansed of its mucosa with water, then rubbed up intimately with powdered silicon, then this mass is expressed by a Buchner press, with which gradually a pressure of 600 atmospheres is reached. From five pig gastric mucosas he thus gained 100 c. c. of a slightly opaque press juice. This is solution **A**. After this has been passed through a Chamberland filter it becomes solution **B**, and when this again is dialyzed for 24 hours in flowing water he obtains solution **C**. Solution **C** is perfectly clear, neutral or very slightly acid, biuret and Millon's reaction positive. Addition of alcohol causes no precipitate, but on addition of ammonium sulphate, acetic acid, picric acid, uranyl acetate, HCl, a cloudiness results. Pepsin digestion is very distinct, and even evident without the addition of HCl. The milk coagulating effect is very energetic. Now comes the important part of Schrumph's preparation. A small amount of cholesterin is added to 10 c. c. of a mixture of ether and absolute alcohol and poured in the remainder of solution **C**. A very dense flocculent precipitate is produced, which is rapidly centrifuged off, thereafter filtered off, and suspended in the original quantity of water. It must then be yet shaken with smaller quantities of ether, which does not make the solution absolutely clear, but it can be made so by passing it through a Kitasato (candle-shaped, Kerzenfilter) filter. Eventually one obtains a perfectly clear filtrate. This is solution **D**. In this solution biuret and Millon's reaction are negative. Acetic acid, picric acid, HCl, uranyl acetate, ammonium sulphate, cause no cloudiness. These reactions, however, can be very distinctly produced in the filtrate obtained after the first removal of the cholesterin precipitate. This solution **D** has a powerful proteolytic effect on addition of 0.2 per cent. HCl. The milk coagulating effect is absent entirely.

The comparative proteolytic and coagulating effects of Schrumph's solutions are the following:

5 c. c.	solution A	digest in 2 hours	3 mm.	Mett;	milkcoagul.	positive
5 "	" " B	" " 2 "	3 "	" "	" "	" "
5 "	" " C	" " 2 "	4 "	" "	" "	" "
5 "	" " D	" " 2 "	8 "	" "	" "	negative.

The supposition that the milk coagulating effect was prevented or obscured in this case by some foreign addition, can

hardly be substantiated in view of the process of preparation. It is probable therefore that Schrumph has prepared a pepsin solution which is free from proteid, has an energetic proteolytic effect, but no milk coagulating effect whatever. If pepsin and chymosin belong to the same molecule, it is to be expected that these two effects stand in a definite and constant relation to each other with regard to their intensity of action. This Pawlow and Parastschuk endeavor to demonstrate by showing up parallelism of effects and proportionality of work done between pepsin and chymosin. Whilst parallelism and proportionality can be considered attributes of an enzyme in which proteolytic and milk curdling effects are due to the same molecule, it does not exactly disprove that the two effects may be due to two different molecules, for we can arrange solutions of two well-known enzymes with characteristic different effects, and still the work done can be demonstrated to have been parallel and proportionate. I base my view that pepsin and chymosin are two different and specific enzymes, or in other words, that the proteolytic and milk curdling effects are due to different molecules, mainly upon the following experiments and observations: (1) Parallelism of effects and proportionality of work done by standardized solutions of two different enzymes artificially produced, or by two different digestive secretions; (2) Parallelism and proportionality as above defined observable in the effects of two different inorganic catalyzers, such as colloidal, platinum, and colloidal silver or gold; (3) The presence of only one of these effects, the proteolytic, and the absence of the milk curdling effect, in certain conditions of the human gastric mucosa; (4) The experiments of Ivar Bang and Schrumph, already described.

In experiments with milk coagulation which extend over 10 hours it must not be overlooked that milk may coagulate spontaneously even when drawn and preserved under absolutely sterile conditions. Pawlow and Parastschuk, in attempting to demonstrate that proteolytic and milk coagulating effects are attributable to one and the same enzyme, offer as proof of their assertion the parallelism of effects and proportionality of work done — the degree of proteolysis was measured in millimeters of a column of boiled albumen (Mett's method, devised in Pawlow's laboratory), and the degree of coagulating power was measured by the time that was required to coagulate 10 c. c. of

milk by varying amounts of gastric juice. The coagulation of the milk always occurred in an acid reaction. The acidity of the various portions of the gastric juice was equalized by 0,5 solution of HCl. In table I (l. c., p. 417), Pawlow demonstrates that the least chymosin was secreted when the test food was milk (10 c. c. of milk coagulated in 50 minutes), and most chymosin was secreted when the test food was bread (10 c. c. of milk coagulated in 2.5 minutes by the bread juice of the same animal). This same juice digested 5.8 millimeters of albumen column (Mett), showing that the proteolytic power was very active also in the same bread juice.

But on page 418, Table II, we are told that a bread juice which digested 5.8 millimeters, did not coagulate 10 c. c. of milk until 3 minutes and ten seconds had elapsed (65 seconds longer than the previous juice which had digested the same length of albumen column). In table II the coagulation time is approximately the same for bread, meat, and milk juice, 190 to 195 seconds, but the relative concentration of the ferments is placed at 1 for bread juice, 4,29 for meat juice, and 8,41 for milk juice. On page 419, the authors assert that this table II shows a perfect proportionality of proteolytic effects and of milk curdling power. The further efforts of these investigators were directed towards showing a parallelism of these two effects of gastric juice under the influence of (a) putrefaction of the juice, (b) the influence of heat, table V, and (c) the influence of chemicals, salts, bile, alcohol etc. Similar experiments are then narrated concerning pancreatic juice obtained in various manners. It is interesting to learn that the pancreatic juice as secreted was inactive for curdling milk, and had to be activated by the addition of succus entericus, and that the activation of the milk curdling agent occurs at the same rate as the activation of the proteolytic agent, under the influence of succus entericus.

On page 432 we are told that table XII, which shows the proteolytic power and milk coagulating power of juice (1) from gastric pepsin glands, (2) from pylorus glands, and (3) from Brunner's glands — gives the evidence that the two powers correspond perfectly. Table XII, however, does not show this convincingly. In column 2 of that table the proteolytic power is shown to sink from 2,5 mm Mett for pepsin gland juice, to 0,5 mm Mett for Brunner's gland juice. But the milk coagulating time for pepsin gland juice is 27 minutes, for Brunner's



gland juice it is 18 minutes. In order to show an exact proportionality, the milk ought to have been coagulated in the same periods of time, as is shown in table II, p. 418. But it is apparent from this table XII that as the proteolytic power sank, the coagulating power became intensified. A possibly involuntary distinction is made between these two effects on page 439, where dilution is said to favor the proteolytic power, restoring it when it had been destroyed, by the sodium acetate (criticism of Glässner's experiments in *Beitr. z. chem. Physiol. und Pathol.*, Bd. I, 1901). But on the other hand dilution is said to destroy the coagulative power. A reduced proteolytic power and the checking influence of salts, or dilution, does not necessarily indicate that the ferment is present in smaller quantities. It may be that the substance which is to be acted upon proteolytically, the albumen of the fibrin, is so altered by the salts or other substances employed as to render them more insoluble. This can be demonstrated by performing experiments with known strengths of pepsin, allowing it to act first upon ordinary pure fibrin, and then upon fibrin which has been allowed to become saturated in a 20 per cent solution of sodium acetate and thereafter washed in distilled water. The proteolysis will be markedly less in the last case.

In the most recent edition of *Lehrbuch der physiolog. Chemie*, Hammarsten objects to the main conclusion of Pawlow and Parastschuk that the two effects spoken of are due to one and the same enzyme, on the ground that two different rules exist according to which these two effects depend upon the quantity of ferments. According to Pawlow, however, the time of these reactions varies with the conditions influencing them. Some may accelerate and others may prolong the time of reaction. The chief conditions which he cites are alkalinity, acidity of the medium, and the degree of dilution (concentration). The authors recognize three rules under such conditions. A neutral solution of chymosin causes milk coagulation provided it is present in the solution in a certain definite concentration; (1) then coagulation occurs according to the rule of inverse proportionality between the quantity of the ferment and the coagulation time; (2) when the chymosin is in acid solution the quantities of the ferment are inversely proportional to the square root of coagulation time, that is, the reaction is progressively accelerated; (3) in a very much diluted neutral solution of ferments the quantities of

the enzymes are porportional to the squares of the coagulating time. These three varying conditions concern mainly the milk coagulating power. In a similar way Pawlow shows that the rules of the dependence of the effects of enzymes upon the amounts of the exzymes can be influenced by external conditions. All such rules are reliable only within very narrow limits.

After reading the article as very briefly abstracted in the preceding, we are justified in asking whether parallelism of effects and proportionality of work done in two different catalytic actions, really constitute satisfactory proof that the two actions are due to one and the same catalyzer. Pawlow and Parastschuk demonstrate that the proteolytic and milk curdling effects of pancreatic juice show a parallelism and proportionality under varying conditions. But the same can be shown to be true of the amylolytic and fat-splitting power of pancreatic juice. Why then not assert that the amylolytic and lipolytic effects are due to one and the same enzyme also? In the American Journal of Physiology, Vol. X, p. 191, Hugh Neilson has shown that colloidal platinum, like lipase, can bring about hydrolysis and synthesis of fats. He also shows that this hydrolysis by platinum increases with the concentration of the platinum, it increases with the temperature, it is independent of the concentration of the ethyl butyrate, and that poisons (see table, l. c., p. 197), reduce the hydrolysis by platinum black. This same variation of effects, under the influence of concentration, temperature, poisons and salts, can be shown to exist with regard tho the effects of a number of organic enzymes. For example, in case of saliva it can be shown that the amylolytic action, the conversion of starch into dextrose, is increased by concentration of the ferment, it is increased by heat, it is injured by certain chemicals, almost in the same manner as lipase is injured in its hydrolysis of ethyl butyrate (experiments of Kastle and Loevenhart, American chemical journal). If, therefore, we should execute a series of experiments in two series, ohne with colloidal platinum on ethyl butyrate under these varying conditions, and the other with saliva and boiled starch under varying conditions, certainly an exactly similar rising or falling of the amount of catalytic work done, that is, a parallelism of effects, could not be asserted as being due to one and the same catalyzer in this case, for we know that two different agants are used in the experiments. The figures

of the hydrolytic effect of colloidal platinum can give in the article by Hugh Neilson (l. c.).

When chymosin or rennet is separated from the stomach of a calf by Blumenthal's method (see J. Reynolds Green, „The Soluble Ferments“, Cambridge Natural Science Manual, 1899, p. 237), an amorphous white gelatinous substance is gained, which greatly resembles aluminum hydrate in appearance. This precipitate in nearly pure rennet, and a very small portion of it speedily causes coagulation of milk. It has no odor or taste when prepared by this method, it readily dissolves in water, forming a clear solution. Blumenthal asserts that the same treatment will separate two enzymes from the so-called pepsin essences of commerce, and that the mother liquid from which the rennet is removed has no curdling action. The trypsin and chymosin of the pancreatic juice were separated by Roberts, a salt solution extract of a pancreas was slightly acidulated with HCl and kept at 40° C. for three hours. When neutralized it was found that the trypsin had been destroyed, while the rennet or chymosin was unharmed.

W. D. Halliburton and Brodie draw a distinction between gastric and pancreatic rennet which has not been noted by previous observers. According to them the clotting indicated by pancreatic rennet is not a true coagulation, but a precipitation which takes place in a warm bath at 35°—40° C. The precipitate is finely granular, and cannot be detected by the naked eye. On cooling it to the temperature of the air, it sets into a coherent curd which can be again broken up by warming to 35° C., when the granular condition returns, and the milk appears fluid. This may be repeated several times. Halliburton and Brodie call the proteid in this condition „pancreatic casein“, and they say it can be converted into tyrein by gastric rennet.

The chymosins of different animals are not identical, and the chymosin of different organs in the same animal, as Halliburton and Brodie have shown, are not identical. The differences in the chymosins of various animals are considerable (Ivar Bang, Pflüger's Archiv, Bd. 79, p. 425). Most of the experiments with chymosin or rennet made prior to the publication of Pawlow and Parastschuk, were made with the chymosin of the calf's stomach, and not until a comparative quantitative study of the various chymosins has been made, can it be proven that the milk coagulating power of all chymosins are alike, or

that this power is governed by the same rule with all forms of this ferment. Dilution, for instance, affects the milk curdling power of chymosin from the pig in a different manner from the chymosin obtained of the dog's stomach. For comparing the effects of their chymosins with the results of previous investigations, it would have been necessary for Pawlow and Parastschuk to use the chymosin of the same animal. Pawlow and Parastschuk, in attempting to prove that proteolysis and milk curdling effects are due to one and the same enzyme, laid greatest stress upon the demonstration of parallelism of effects under various chemical and physical influences, and secondly upon proportionality of work done. To subject a digestive secretion that gives evidence of two strikingly different effects to varying external influences, and thereby showing that the effects increase and diminish together, or disappear together, can hardly be considered a satisfactory form of experimental logic to prove that these two different effects are due to one and the same agent. The work of these authors proves that the technique and method of experimentation may be objective and perfect, and yet the subjective deduction therefrom may be capable of different interpretations. In order to make clear my meaning I will cite the example of two well-known digestive enzymes, the actions of which occur best in a mildly alkaline medium, ptyalin of the saliva, and trypsin of the pancreatic juice. Trypsin prepared by Kühne's method (*Unters. a. d. physiol. Institut der Universität Heidelberg*, Bd. I, 222), and ptyalin both can be shown to be augmented and inhibited in their characteristic effects upon fibrin and boiled starch respectively in a parallel manner by temperature, by chemicals and poisons, by concentration and dilution. The amount of ptyalin and the amount of boiled starch in the one case, and the amount of trypsin and the proteid upon which it acts, either fibrin or boiled egg albumen, can be so adjusted that a parallelism of effects and proportionality of work done can be shown to exist between these two ferments. If the same logic were applied to these phenomena as Pawlow and Parastschuk apply to milk curdling and proteolysis, it would be equally possible to assert the amylolysis and proteolysis to be due to one and the same enzyme, if it were not positively known beforehand that two definite enzymes were employed. The method employed in Pawlow's laboratory



to determine the degree of amylolysis is similar to that of Mett for proteolysis. Mett tubes are employed which are filled with filtered egg albumen coagulated in a water bath, and sealed at both ends with sealing wax. For amylolysis the tubes are filled with boiled starch in a similar manner. The diastatic power is expressed by the number of millimeters of boiled starch digested in a given time. In most of my work I employed pancreatic juice obtained from the duct of Wirsung of the dog.

Experiments with dog saliva and pancreatic juice trypsin (Kühne), demonstrating effects of increase of temperature. On digestion of boiled starch and albumen respectively.

Canine saliva and trypsin solutions were subjected in different and separate portions to the various temperatures stated in column 1, and thereafter their amyolytic and proteolytic power tested.

Temperature.	Saliva.	Pancreatic juice
	No. of m.m of boiled starch column digested by.	trypsin. No. of m.m of albumen column digested.
10° C.	4,20	5,52
12° C.	4,15	5,5
15° C.	4,25	5,9
20° C.	4,25	6
30° C.	5,1	6,5
40° C.	4,95	5,9
50° C.	3,5	4,5
52° C.	2,75	3,62
54° C.	2	3
56° C.	0,5	0,9
58° C.	0,3	0,5
60° C.	0	0
62° C.	0	0
64° C.	0	0

Both enzymes exhibit a first a slight increase of their characteristic effects followed by a gradual diminution until the enzymes are completely destroyed at 60° C., a parallelism of effects — which can also be demonstrated if both saliva and trypsin solution are poured together and a starch, as well as an albumen tubule, placed in the combined solution simultaneously. But here the action of amylopsin requires exclusion.

The following tables demonstrate the gradually reducing effect of the chymosin and pepsin, and also the changes in the free HCl and total acidity in gastric juices drawn from human patients, It will be seen from these tables that parallelism of effects and proportionality of work done are as a rule not evident. The cases „Pyle“, „Ward“ and „Weinberg“ were cases of gastritis acida, those of „Cartridge“, „Hamilton“ and „Dawkins“ were cases of hyperchlorhydria (nervosa), the case of „Warner“ was one of dilatation of the stomach, and the case of „Spencer“ was one of hyperchlorhydria.

Tests for any change of acidity values in the human gastric juice on standing at room temperature.

Ward.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 0,2 cc. gastric juice in minutes
November 16	34	48	5	3' 15"
" 17	31	47	5	3' 15"
" 18	34	48	5	3' 15"
" 19	34	48	5	3' 15"
" 21	32	48	5	3' 15"
" 22	32	48	5	3' 15"
" 23	34	48	5	3' 15"
" 24	32	50	5	3' 10"
" 25	32	50	4,5	3' 20"
" 26	32	50	4,5	3' 20"
" 28	34	49	5	3' 24"
" 29	32	48	4,5	5'
" 30	32	50	4,5	5'
December 1	31	48	4	5'
" 2	32	48	3,5	6'
" 3	32	49	3,5	8'

Weinberg.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 1 cc. gastric filtrate in minutes
November 17	39	62	4,5	3'
" 18	42	64	4	3' 30"
" 19	44	63	4,5	3'
" 21	42	65	4	3'
" 22	42	66	4,5	3' 30"
" 23	41	70	4	3'

Pyle.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 1 cc. gastric filtrate in minutes
November 22	29	64	4,5	3' 30"
" 24	29	64	4,5	4'
" 25	30	66	4,5	4'
December 1	30	65	4,5	3' 50"
" 2	31	65	4,5	3' 50"
" 3	30	64	4,5	3' 50"
" 4	30	65	4,5	3' 50"
" 5	31	66	4,5	3' 50"
" 6	30	64	5,5	3' 20"
" 7	31	65	5,5	3' 20"
" 8	31	64	5,5	3' 20"
" 9	31	64	5,5	3' 20"
" 10	32	64	5	3' 20"

Cartridge.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 0,2 cc. gastric filtrate in minutes
January 17	74	100	8	5'
" 18	76	104	8	5' 10"
" 20	76	108	8	5' 10"
" 23	74	104	8	5'
" 25	74	104	8	5' 10"
" 26	76	104	8,5	5'
" 26	72	102	7	4' 20"
" 30	78	106	7,5	4' 30"
" 31	74	106	6	4'

Increasing cloudiness of gastric filtrate made the exact time of turning of the dimethyl amido benzol more difficult to recognize as the filtrate became older. The free HCl was then ascertained in other specimens by the Hoffman method (dissociation of methyl acetate) with same results.

Increasing cloudiness of gastric filtrate made the exact time of turning of the dimethyl amido benzol more difficult to recognize as the filtrate became older.

Same gastric juice of Spencer, when left in incubator at 36° C., began to lose its proteolytic power in 20 days. The milk

Hamilton.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 1 cc. gastric filtrate in minutes
1904 December 30	65	110	6,5	4'
1905 January 3	60	110	6	4' 10"
" 5	64	116	6,5	4'
" 7	66	120	6,5	4'
" 10	70	124	7	3' 10"
" 12	62	120	6	3' 40"
" 14	74	118	6	3' 40"
" 18	68	118	6,5	3' 45"
" 20	70	120	7	3' 10"
" 22	66	118	6,5	4'
" 26	68	118	6,5	4'

Dawkins.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 2 cc. gastric filtrate in minutes
1905 January 25	60	90	5	1'
" 28	62	100	4,5	1'
" 30	62	88	5	1' 5"
February 1	62	88	4,5	1' 5"
" 4	62	98	4,5	1' 15"
" 6	60	96	5	1' 5"
" 8	60	100	5	1' 5"
" 10	62	110	5	1' 5"
" 14	62	105	5	1' 5"
" 18	62	100	5	1' 5"

curdling power diminished more rapidly and disappeared entirely on the eighteenth day.

From Spencer a very large test meal was drawn, amounting to 760 c. c. of gastric chyme, which was kept under experimentation 56 days. In this table the figures show the proteolysis to diminish gradually from 8 mm. on January, to 4 mm. on February 28, but the milk coagulating power diminishes more rapidly and out of all proportion to the rate in which the proteolytic power diminishes. No parallelism in the diminution of these effects is here detectable.



Warner.

Date	Free HCl	Total Acidity	Proteolysis in mm. Mett tubes	Chymosin, 10 cc. milk coagulated by 2 cc. gastric filtrate in minutes
1905				
February 1	26	66	3	5' 0"
" 2	24	70	3	5' 0"
" 4	24	72	3	5' 0"
" 6	26	74	3	5' 0"
" 8	26	72	3	5' 0"
" 10	26	72	3	8' 0"
" 14	28	72	3,5	8' 30"
" 16	26	70	3,5	10' 15"
" 20	28	70	3,5	10' 15"
" 21	26	68	3,5	11' 0"
" 24	28	70	3,5	12' 0"
" 26	28	68	3,5	15' 10"

One of the most interesting facts discoverable during persistent analyses of human gastric juice is the total absence in some of them of the milk curdling enzyme, whilst at the same time the peptic or proteolytic enzyme is present. This is proven by the fact that whilst the filtrate from test meals consisting of bread and water will not curdle milk, it will give the biuret reaction when it is added to disks of boiled egg albumen or fibrin thereafter placed in the digestorium. This occurs in certain stages of chronic atrophic gastritis, when the milk curdling enzyme disappears before the peptic enzyme. I have also seen it in two cases of cancer of the stomach. I must emphasize, however, that I have studied the gastric juice of two persons who were normal to all subjective and objective examinations. I have frequently, in order to emphasize the fact that the milk curdling enzyme is absent, poured a pint of milk into the stomach of one of these persons, and withdrawing it by the stomach tube an hour and 20 minutes thereafter, in the identical condition in which it was poured down through the stomach tube. Nor did this milk coagulate after it was allowed to stand in an incubator for three hours. Nor could it be made to coagulate in less time than three hours by the addition of varying amounts of calcium carbonate, nor by the addition of 1/10 normal solution of HCl added until the normal amount which should be present in the

Spencer.

Date	Free HCl (Töpper's Method)	Total Acidity	Proteo- lysis in mm. Mett tubes	Chymosin, 5 cc. sterile milk coagulated by 2 cc. gastric filtrate in minutes
1905				
January 3	60	64	8	30"
" 4	60,5	66	8	30"
" 5	60,6	64	8,5	20"
" 6	61	66	8,5	30"
" 7	60	66	8	30"
" 9	60	64	8	30"
" 12	61	65	8	30"
" 14	60,5	65	8	30"
" 15	61	66	8,5	30"
" 18	61	65	8	30"
" 20	66	60	8	30"
" 21	65	60	8,5	30"
" 24	65	59,5	8	30"
" 26	65	59,5	7,5	1' 8"
" 28	65	60	7,5	1' 8"
" 30	60	65	7,5	1' 8"
" 31	59	65	7,5	1' 8"
February 1	60	65	6	1'
" 3	59	66	5,5	1' 2"
" 6	59	66,5	5	1' 2"
" 10	58	67	5	2'
" 14	57	68	5	3' 5"
" 16	55	67,5	5	3' 5"
" 18	50	68	4,5	4' 0"
" 20	50	69	4,5	5' 5"
" 22	48	70	4	10'
" 24	48	72	4	12' 5"
" 28	46	74	4	20' 5"

gastric juice is reached. Milk to which HCl is added in this manner will coagulate when no enzyme is present but it takes a much longer time (10—16 hours). Gastric juice which was boiled, and thus had its enzymes destroyed, did not coagulate milk any sooner than a solution of HCl of the same strength. In testing milk coagulation on the addition of HCl, the time in which the coagulation occurs is an important factor in the determination. The same persons whose gastric juice could not curdle milk produced a feeble proteolytic enzyme, for the filtrate from an Ewald test meal gave the biuret reaction. This conclusion is based upon the assumption that the biuret reaction is an indication of the presence of peptones. These gastric juices, although they give no evidence of presence of HCl to the ordi-

nary color tests (Acid indicators), showed a feeble dissociation of methyl acetate by the Hoffmann-Ostwald method of determining the free HCl. This probably indicates that the HCl may be so loosely combined with proteoses and acid albumen, that it can readily dissociate and in the presence of pepsin produce peptones, although the ordinary color tests — congo red tropaeolin 00, phloroglucin-vanillin —, are negative.

We had in these persons a demonstration of gastric juices that (1) contained no free HCl, but combined HCl, because they were capable of producing biuret reaction; (2) could not coagulate milk; (3) they gave the biuret reaction with an Ewald test meal. The conclusion seems justifiable that pepsin was present, but rennin or chymosin was absent, which is difficult to harmonize with the view of Pawlow that the proteolytic and the milk curdling effects are due to one and the same molecule.

#### Schlussätze zu obiger Arbeit.

Zu Gunsten seiner geistreichen Hypothese, dass die proteolytische und milchgerinnende Wirkung verschiedener Verdauungssäfte nicht verschiedenen, sondern ein und demselben Molekül angehören, führt der hochverdiente Forscher (Pawlow) weiter an (l. c. p. 449):

I. Dass die Milchkoagulation eine Komplikation des Eiweissmoleküles sei, ganz entsprechend der Vereinfachung desselben, welche unter Einwirkung der proteolytischen Fermente, wie Pepsin, stattfindet und citiert die Untersuchungen von A. Danielowsky und Okunew, nach welchen Koagulation einiger Albumosen durch Labfermente nachgewiesen worden seien.

Dass zur Demonstration einer solchen Annahme vorerst die Darstellung eines reinen Labfermentes nötig ist., d. h. ohne die Wirkung eines Eiweissferments zugleich zu besitzen, ist evident. Aber in jener ganzen Arbeit ist doch das Hauptargument, dass solche exklusiv Labwirkung aufweisende Enzyme nicht vorkommen.

Die reversible Wirkung von einem Fermente ist zuerst von Loewenhardt und Kastle (American Chemical Journal) nachgewiesen worden und zwar die zerspaltende und zugleich synthetische Wirkung der Lipase auf das Athylum butyricum. Mit solchen relativ einfachen Körper (substrat) arbeitend, lässt sich einwandfrei bei der Lipase zugleich analytische und synthetische Wirkung nachweisen.

Beweisen aber die interessanten Arbeiten von Danilewsky und Okunew in der Tat, dass eine Koagulation von Albumosen durch reines Labferment vorkommt? Ist es nicht eine Präzipitation und keine Koagulation? Wie man analog ein Präzipitin streng von einem Koagulin zu unterscheiden hat.

Auffallend ist es, dass, wenn den proteolytischen Enzymen der Verdauungssäfte zugleich auch koagulierende Eigenschaften zukommen sollen, diese letztere Wirkung sich nur an einem Proteid demonstrieren lässt (der Milch, nämlich Kasein). Wenn das eine allgemeine Qualität solcher Fermente wäre, müsste es sich doch auch an anderen Eiweisskörpern demonstrieren lassen. Um reversible Effekte eines Fermentes zu demonstrieren, müssen beide Wirkungen an ein und demselben Proteid bewiesen werden. In dem Falle der Verdauungssäfte scheitert diese Bedingung, denn das Pepsin kann man nur durch seine analytische Wirkung auf Eiweiss beurteilen (Mett'sche Methode), die hypothetische synthetische Wirkung jedoch nur auf das Proteid der Milch.

II. Eine weitere Begründung ihrer Annahme suchen die Herren Professor Pawlow und Dr. Parastchuk darin, dass Labferment bei verschiedenen Tieren und Pflanzen vorkommt, wo es niemals mit Milch in Berührung kommt, und erheben die Frage: Wozu?

Hier wird nun der Zweckbegriff in die Diskussion eingeführt und als Argument benutzt. Wenn in der Tat Lab bei Tieren und Pflanzen vorkommt, wo es niemals mit Milch in Berührung kommt, so ist die Frage: Wozu? schwer zu beantworten. Die genannten Forscher wollen zu verstehen geben, dass eben Chymosin und Pepsin identisch sind (ist Pepsin vorhanden, dann ist Labwirkung ebenfalls nachzuweisen). Nun gibt es aber auch proteolytische Enzyme in Pflanzen, wo es niemals mit zu verdauendem Proteid in Berührung kommt, in dem Saft der reifen Ananas zum Beispiel. Ich habe mit dem Saft der Ananas gearbeitet und einer meiner Assistenten mit dem Saft der Suavaf Frucht. Obschon beide Säfte Milch koagulieren (ein Tropfen Ananassaft bringt 20 cem Kuhmilch in 15 Minuten zur Gerinnung), konnten wir uns nicht überzeugen, dass diese Wirkung von einem Ferment abhing. Denn erstens waren beide Fruchtsäfte intensiv sauer, und neutralisierten wir die Säure, dann hoben wir die Labwirkung auf. Und zweitens vertrugen die Säfte einen höheren Grad der Erhitzung (70° C.) als dem Lab für gewöhnlich d.h. ohne Zerstörung zuträglich, zugeschrieben wird. Pawlow und Parastschuk würden vielleicht den Verlust der Milchge-



rinnung bei der Neutralisation einer Hemmung des Labs durch die angewandte Decinormallösung von NaOH oder KOH zuschreiben oder einer Erhöhung der Salzkonzentration, doch konnte eine darauf folgende Verdünnung die Labwirkung nicht wieder herstellen.

Eine sehr interessante Stütze der Ansicht, dass Pepsin und Chymosin nicht identisch, sondern zwei spezifische Fermente sind, liesse sich auf biochemischem Wege erzielen. Es ist vielleicht nicht logisch, durch Untersuchungen, die noch nicht vollendet sind, etwas beweisen zu wollen. Doch kann ich als vorläufige Mitteilung nicht unterdrücken, mitzuteilen, dass das auf biochemischem Wege von Serum gewonnene Antilab nicht auch zugleich ein Antipepsin ist, was doch der Fall sein müsste, wenn das dem Tier injizierte Pepsin als Ferment ein chemisch einheitliches Molekül darstellte.

Auf biochemischem Wege steht auch die Vermutung nahe, dass die Labfermente der Säugetiere verschieden sind, denn ein Antilab durch Injektion des aus Kälbermagen gewonnenen Ferments (Methode nach Ivar Bang) erzielt, hebt die milchkoagulierende Wirkung von Hundelab nicht auf.

Ich habe bisher nur mit den Enzymen aus Magen von Hunden, Meerschweinchen, Katzen, Kälbern und Schweinen gearbeitet und sie mit den Enzymen aus menschlichen Magensäften verglichen und habe den Eindruck gewonnen, dass das Lab eines jedes dieser Tiere spezifisch am effektivsten auf die Milch desselben Tieres koagulierend wirkt.

Hat man aus Meerschweinchenserum ein Antilab gewonnen, welches durch Injektion von Kälberlab erzeugt wurde, so ist die hemmende Wirkung des Antilabs am effektivsten mit der Kuhmilch zu demonstrieren, d. h. mit der Milch der Tiergattung, von welcher das Lab ursprünglich genommen wurde. Diese feinen Unterschiede berechtigen zu der Ansicht, dass „reciproke“ biochemische Beziehungen zwischen den verschiedenen Labarten und Milcharten bestehen.

Alle diese Beobachtungen sollen jedoch nicht als Ablehnung der herrlichen Arbeiten Pawlow's gelten, sondern nur betonen, dass die vielbesprochene Identität des Pepsins und Labs noch nicht endgültig bewiesen ist. Das Denken dieses geistreichen Physiologen hat bisher so wunderbar befruchtend gewirkt, dass sicher weitere wertvolle Beiträge von ihm zu erhoffen sind.





# THE HOSPITAL BULLETIN

BALTIMORE, MD. NOVEMBER 15, 1905.

## NON-DIGESTION OF NUCLEI IN MEAT FIBER: A CRITERION OF PANCREATIC DISEASE (INSUFFICIENCY).

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It is known from the interesting investigations of Prof. Adolf Schmidt that raw connective tissue can only be digested by the gastric juice, while the nuclear substance of meat fiber can only be digested by pancreatic juice. Hence the appearance of remnants of undigested connective tissue in the feces points to the insufficiency or absence of gastric secretion; and the appearance of nuclei cells in meat fibers is significant of insufficient secretion of pancreatic juice. Personally, I have tested the first deduction of Dr. Schmidt in eight cases of "achylia gastrica" and six cases of chronic "atrophic gastritis" with entire absence of free or combined HCl ferments. In all eight cases of achylia gastrica and in five cases of atrophic gastritis the undigested connective tissue fibers were found in the feces. In two cases of heterochylia (i. e., variable gastric secretion) hyperchlorhydria with excess of pepsin and chymosin alternating with absolute achylia in the same person after the identical test-meal. (See Ueber Heterochylie. (Hemmeter) von George Korn, Archiv f. Verdauungskrankheit. Bd. vii, 1902, S. 75). The undigested connective tissue fibers were found in the feces only during the periods of absolute achylia, when the gastric juice contained no ferments nor free or combined HCl. They disappeared from the feces in periods during which the gastric juice was normal. Two of these cases of heterochylia I have had under observation off and on for eight years; their feces and gastric contents were examined during a period of five or six weeks in the spring and fall of each year.

I might add that during the periods of absence of HCl and enzymes in the gastric juice no biuret reaction could be obtained in the gastric filtrates,

but the addition of 10 cubic centimeters of officinal dilute hydrochloric acid, together with one grain of pepsin diluted with distilled water to represent the concentration of hydrochloria in gastric juices, caused perfect digestion of connective tissue if persisted in for 48 hours; that is, at 0.2 per cent. (two per mille) solution of HCl with sufficient pepsin to approximate the concentration (amount) in gastric juice will cause disappearance of undigested connective tissue fibers from the stool. The amount of pepsin to be added varies with different meals, but cannot be definitely stated a priori. It should be added to gastric filtrate or chyme (10 c. c.) until the reaction of free HCl appears on titration with Congo and the Phloroglucin-vanillin test. Sometimes it is impossible for the patient to swallow such large quantities of dilute HCl. Then we occasionally succeed by giving the requisite amount of officinal HCl in large gelatine capsules, and directing the patient to drink the corresponding amount of water afterwards.

For studying the conditions of pancreatic secretion by means of its effects on the nuclear substance of meat fiber, Adolf Schmidt uses slightly fibrous beef, which is cut into small cubes of 0.5 cm. square, and preserves them in absolute alcohol. Prior to using them as tests they are immersed in water for three hours and given to the patient in wafers. The test diet which Schmidt recommends (Funkions prüfung der Darms mittelst Probekost, Wiesbaden, 1904) must be faithfully adhered to, and does not impose any inconveniences upon the patient. Personally I make use of an improved Boas stool sieve for regaining the little silk sacs. If the cases have any pancreatic disturbances, there must, of course, be remnants of muscle in the sacs. In the sifted stools of 12 healthy students no muscle remnants were ever found in 30 different tests. If muscle remnants are found they are washed in water, hardened in alcohol, sectioned if need be, and stained with nuclear stains. It is not, as a rule, necessary to harden the beef remnants; after rinsing them in water they can be directly treated with dil. acetic acid or methyl blue. Wallenfung studied these beef remnants after they had passed through the entire digestive tracts of dogs that had been deprived of their pancreas. In three dogs that survived total extirpation of the pancreas, the meat fibers regularly contained their nuclei and were readily stainable.

Preservation of the nuclei justifies the conclu-



sion of pancreatic disease, or at least absence of pancreatic juice from the intestines (the two conditions are not always identical) only, if the time of the passage of the meat was of a normal period. A very rapid passage of the sacs, such as occurs in diarrhoea, frustrates the action of the trypsin, even if it is present.

In two cases of pancreatic abnormality this test worked satisfactorily. One was a large pancreatic cyst, compressing and obliterating the duct of Wirsung. A second case was stenosis and adhesions of this duct by an old pericholecystitis, an extension of a preceding cholelithiasis. In the first case the pancreas itself did not appear seriously diseased at the operation; it seemed that its entire secretion was collected into the huge cyst, the contents of which had the same physiologic and chemic properties as a similar case closely studied by me in 1898 (Hemmeter and Adler, "A Chemic and Physiol. Study of Pancreatic Cyst Fluid, etc., New York *Med. Record*, Aug. 6, 1898). Both cases recovered after operation, and six weeks thereafter no nuclei could be discovered in the stools.

Adolf Schmidt believes that his test, when combined with the test of Sahli, will facilitate the diagnosis of pancreatic disease, and if I may speak from my rather limited experience thus far it must be in confirmation of his conclusions.

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Are the Proteolytic and Milk Coagulating Effects of Gastric and Pancreatic Juice Due to One and the Same Enzyme?

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ARE THE PROTEOLYTIC AND MILK COAGULATING EFFECTS OF GASTRIC AND PANCREATIC JUICE DUE TO ONE AND THE SAME ENZYME?\*

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The distinguished St. Petersburg physiologist, J. P. Pawlow, associated with S. W. Parastschuk, has published<sup>1</sup> a series of experimental investigations under the above heading. The view hitherto held and still held by most physiologists is that the proteolytic and milk-coagulating effects of gastric juice and pancreatic juice are due to specific enzymes. The earlier investigations on the subject date from Hammarsten.<sup>2</sup> In order to state precisely the direction of the inquiry, it is necessary to emphasize that Pawlow and Parastschuk attempt to prove that a separate and distinct milk-curdling enzyme does not exist, but that the milk coagulation is only a property of the pepsin. The *Fragestellung* here is not precise as might be desirable, for proteolytic and milk-coagulating effects might be conceived as attributable to one and the same proteid ferment, and yet pepsin and chymozin may be two different enzymes, for we may conceive that pepsin, the proteolytic enzyme, possesses also, to a certain extent, a milk-coagulating effect, which is only developed in an acid reaction and not in a neutral reaction, and, as far as human gastric

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\* Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-sixth Annual Session, July, 1905.

1. Hoppe-Seyler's Zeitsch. f. physiol. Chemie, vol. iv, pp. 415 to 452: "Ueber die ein und demselben Eiweissfermente zukommende proteolytische und milchkoagulierende Wirkung verschiedener Verdauungssäfte."

2. Maly's Jahres Berichte, vol. ii, 1872, p. 118. See also Hammarsten's Lehrbuch der physiol. Chemie, 5th edition.



juices are concerned, it can be stated that such an enzyme occurs which will curdle milk in the presence of an amount of HCl which, as a rule, is normal to human gastric juice (two parts per thousand), but will not curdle milk if the gastric juice is exactly neutralized. This disappearance of milk-coagulating power in the case of canine gastric juice, after it had been neutralized with sodium bicarbonate, was noticed by Pawlow and Parastschuk (p. 422), but they attributed this disappearance to a destructive effect of the alkalies employed, particularly to  $\text{Na}_2\text{CO}_3$ . When the juice was neutralized with  $\text{NaHCO}_3$ , the ferment could be preserved. To the destruction of the pepsin by alkalies they attribute their inability to separate these two enzymes by Hammarsten's method (shaking of gastric juice with magnesium carbonate, by which the pepsin is torn down by this insoluble powder), while the chymozin remains in solution. The third and fourth filtrates prepared in this way will coagulate milk energetically, but will not digest raw fibrin in twenty-four hours, not even if raised to the normal acidity. But Pawlow asserts that when this fibrin was diluted five to ten times its volume with 0.1 to 0.2 per cent. solution of HCl, the proteolytic effect on fibrin became distinctly evident.

The two enzymes, however, can be separated in a much simpler manner; by heating gastric juice to 65 degrees C. for ten minutes the chymozin can be destroyed. When chymozin is in solution together with HCl, three parts per thousand, the enzyme can be destroyed completely if the solution is kept at a temperature of 37 to 40 degrees C. for forty-eight hours.<sup>3</sup> The pepsin is not destroyed by this process. In this manner a pepsin solution free from chymozin can be obtained. A solution of parachymozin free from pepsin can also be prepared in a similar manner.<sup>4</sup> Bang's investigations have made it very highly probable that the chymozin enzymes of different animals are by no means identical, but show striking differences in milk-coagulating power. Accordingly it becomes necessary in testing the results of previous investigators, to use the chymozin from the same animals as they employed.

In experiments with milk coagulation which extend over ten hours it must not be overlooked that milk may

3. Hammarsten, p. 271.

4. Pfüger's Archiv, vol. lxxix, p. 425. Article by Ivar Bang.

coagulate spontaneously when drawn and preserved under absolutely sterile conditions. Pawlow and Parastschuk, in attempting to demonstrate that proteolytic and milk-coagulating effects are attributable to one and the same enzyme, offer as proof of their assertion the parallelism of effects and proportionality of work done. The degree of proteolysis was measured in millimeters of a column of boiled albumin (Mett's method, devised in Pawlow's laboratory), and the degree of coagulating power was measured by the time that was required to coagulate 10 c.c. of milk by varying amounts of gastric juice. The coagulation of the milk always occurred in an acid reaction. The acidity of the various portions of the gastric juice was equalized by 0.5 solution of HCl. In Table 1, Pawlow<sup>1</sup> demonstrates that the least chymozin was secreted when the test food was milk (10 c.c. of milk coagulated in fifty minutes), and the most chymozin was secreted when the test food was bread (10 c.c. of milk coagulated in two and one-half minutes by the juice of the same animal). This same animal digested 5.8 mm. of albumin column (Mett), showing that the proteolytic power was very active also in the same bread juice. But in Table 2 we are told that a bread juice which digested 4.8 mm. did not coagulate 10 c.c. of milk until three minutes and ten seconds had elapsed, forty seconds longer than the previous juice, which had digested the same length of albumin column. In Table 2 the coagulation time is approximately the same for bread, meat and milk juice, 190 to 195 seconds, but the relative concentration of the ferments is placed at 1 for bread juice, 4.29 for meat juice, and 8.41 for milk juice. On page 419 the authors assert that this Table 2 shows a perfect proportionality of proteolytic effects and of milk-curdling power. The further efforts of these investigators were directed toward showing a parallelism of these two effects of gastric juice under the (a) influence of putrefaction of the juice; (b) the influence of heat (Table 5), and (c) the influence of chemicals, salts, bile and alcohol, etc. Similar experiments are then narrated concerning pancreatic juice obtained in various ways. It is interesting to learn that the pancreatic juice as secreted was inactive for curdling milk, and had to be activated by the addition of succus entericus and that the activation of the milk-curdling agent occurs at the

same rate as the activation of the proteolytic agent, under the influence of succus entericus (enter-kinase).

On page 432 we are told that Table 12, which shows the proteolytic power and milk-coagulating power of juice (1) from the gastric pepsin glands, (2) from pylorus glands, and (3) from Brunner's glands, gives the evidence that the two powers correspond perfectly. Table 12, however, does not show this convincingly. In the second column of that table the proteolytic power is shown to shrink from 2.5 mm. (Mett) for pepsin gland juice to 0.5 mm. (Mett) for Brunner's gland juice. But the milk-coagulating time for pepsin gland juice is 27 minutes, for Brunner's gland juice is 18 minutes. In order to show an exact proportionality, the milk ought to have been coagulated in the same periods of time, as is shown in Table 2. But it is apparent from Table 12 that as the proteolytic power sank the coagulating power became intensified. Possibly an involuntary distinction is made between these two effects on page 439, where dilution is said to favor the proteolytic power, restoring it when it had been destroyed by the cold sodium acetate.<sup>5</sup> But, on the other hand, dilution is said to destroy the coagulative power. A reduced proteolytic power under the checking influence of salts, or dilution, does not necessarily indicate that the ferment is present in smaller quantities. It may be that the substance which is to be acted on proteolytically—the albumin or the fibrin—is so altered by the salts or other substances employed as to render them more insoluble. This can be demonstrated by performing experiments with known strengths of pepsin, allowing it to act first on ordinary pure fibrin, and then on fibrin which has been allowed to become saturated in a 20 per cent solution of sodium acetate. The proteolysis will be markedly less in the last case.

Hammarsten<sup>6</sup> objects to the main conclusion of Pawlow and Parastschuk that the two effects spoken of are due to one and the same enzyme, on the ground that two different rules exist, according to which these two effects depend on the quantity of ferments. According to Pawlow, however, the time of these reactions varies with the conditions influencing them. Some may accelerate

5. Criticism of Glessner's experiments in *Beitr. z. chem. Physiol. u. Path.*, vol. i, 1901.

6. *Lehrbuch der Physiolog. Chemie.*

and others may prolong the time of reaction. The chief conditions which he cites are alkalinity, acidity of the medium, and the degree of dilution. The authors recognize three rules under such conditions. A neutral solution of chymozin causes milk coagulation provided it is present in the solution in a certain definite concentration: (1) Then coagulation occurs according to the rule of inverse proportionality between the quantity of the ferment and the coagulation time; (2) when the chymozin is in acid solution the quantities of the ferment are inversely proportional to the square root of coagulation time, that is, the reaction is progressively accelerated; (3) when, in a very much diluted neutral solution of ferments, the quantities of the enzymes are proportional to the square of the coagulation time. These three varying conditions concern mainly the milk-coagulating power. In a similar way, Pawlow shows that the rules of the dependence of the effects of enzymes on the amounts of the enzymes can be influenced by external conditions. All such rules are reliable only within very narrow limits.

After reading the article as abstracted, we are justified in asking whether parallelism of effects and proportionality of work done in two different catalytic actions, really constitute satisfactory proof that the two actions are due to one and the same catalyzer. Pawlow and Parastschuk demonstrate that the proteolytic and milk-curdling effects of pancreatic juice show a parallelism and proportionality under varying conditions. But the same can be shown to be true of the amylolytic and fat-splitting power of pancreatic juice. Why, then, not assert that the amylolytic and lipolytic effects are due to one and the same enzyme also? Neilson<sup>7</sup> has shown that colloidal platinum, like lipase, can bring about hydrolysis and synthesis of fats. He also shows that this hydrolysis by platinum increases with the concentration of the platinum, increases with the temperature, is independent of the concentration of the ethyl butyrate, and that poisons<sup>8</sup> reduce the hydrolysis by platinum black. These same variations of effects, under the influence of concentration, temperature, poisons and salts, can be shown to exist with regard to the effects of a number of organic

7. *Am. Jour. Physiol.*, vol. x, p. 191.

8. *Ibid.*, table, p. 197.



enzymes. For example, in the case of saliva it can be shown that the amylolytic action, the conversion of starch into maltose, is increased by concentration of the ferment, and by heat, but is injured by certain chemicals almost in the same manner as lipase is injured in its hydrolysis of ethyl butyrate (experiments of Loevenhart). If, therefore, we should execute a series of experiments in two series, one with colloidal platinum on ethyl butyrate under these varying conditions, and the other with saliva under varying conditions, certainly a rising or falling of the amount of catalytic work done, that is, a parallelism of effects, could not be asserted as proving that the two different effects are due to one and the same catalyzer in this case, for we know that two different agents are used in the experiments. The figures of the hydrolytic effect of colloidal platinum are given in the article by Hugh Neilson.<sup>7</sup>

When chymozin or rennet is separated from the stomach of a calf by Blumenthal's method,<sup>9</sup> an amorphous, white, gelatinous substance is gained, which greatly resembles aluminium hydrate in appearance. This precipitate is nearly pure rennet, and a very small portion of it speedily causes coagulation of milk. It has no odor or taste when prepared by this method, readily dissolves in water, and forms a clear solution. Blumenthal asserts that the same treatment will separate two enzymes from the so-called pepsin essences of commerce, and that the mother liquid from which the rennet is removed has no curdling action. The trypsin and chymozin of the pancreatic juice was separated by Roberts. A salt solution extract of a pancreas was slightly acidulated with HCl and kept at 40 degrees C for three hours. When neutralized, it was found that the trypsin had been destroyed, while the rennet or chymozin was unharmed.

W. D. Halliburton and Brodie draw a distinction between gastric and pancreatic rennet which has not been noted by previous observers. According to them the clotting indicated by pancreatic rennet is not a true coagulation, but a precipitation which takes place in a warm bath at 35 to 40 degrees C. The precipitate is finely granular and can not be detected by the naked eye. On cooling it to the temperature of the air, it sets into a coherent

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9. J. Reynolds Green, *Soluble Ferments, etc.*, Cam. Nat. Sci. Man., 1899, p. 237.

curd which can be again broken up by warming to 35 degrees C., when the granular condition returns, and the milk appears fluid. This may be repeated several times. Halliburton and Brodie call the proteid in this condition "pancreatic casein," and they say it can be converted into tyrein by gastric rennet.

The chymozins of different animals are not identical, and the chymozins of different organs in the same animal, as Halliburton and Brodie have shown, are not identical. The differences in the chymozins of various animals are considerable.<sup>10</sup> Most of the experiments with chymozin or rennet made prior to the publication of Pawlow and Parastschuk were made with the chymozin of the calf's stomach, and not until a comparative and quantitative study of the various chymozins has been made can it be proved that the milk-coagulating power of all chymozins is alike, or that this power is governed by the same rule with all forms of this ferment. Dilution, for instance, affects the milk-curdling power of chymozin from the pig in a different manner from the chymozin obtained from the dog. For comparing the effects of their chymozin with the results of previous investigations, it would have been necessary for Pawlow and Parastschuk to use the chymozin from the same animal.

Pawlow and Parastschuk, in attempting to prove that proteolysis and milk-curdling effects are due to one and the same enzyme, laid greatest stress on the demonstration of parallelism of effects under various chemical and physical influences, and, secondly, on proportionality of work done. To subject a digestive secretion that gives evidence of two strikingly different effects to varying external influences, and thereby showing that the effects increase and diminish together, or disappear together, can hardly be considered a satisfactory form of experimental logic to prove that these two different effects are due to one and the same molecule. The work of these authors proves that the technic and method of experimentation may be objective and perfect, and yet the interpretation or subjective deduction therefrom may be unsatisfactory.

In order to make clear my meaning I will cite the example of two well-known digestive enzymes, the actions of which occur best in a mildly alkaline medium, ptyalin

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10. Pflüger's Archiv., vol. lxxix, p. 425.

of the saliva, and trypsin of the pancreatic juice. Both trypsin prepared by Kühne's<sup>11</sup> method and ptyalin can be shown to be augmented and inhibited in their characteristic effects on fibrin and boiled starch, respectively, by temperature, by chemicals and poisons, by concentration and dilution. The amount of ptyalin and the amount of boiled starch in the one case, and the amount of trypsin and the proteid on which it acts, either fibrin or boiled egg albumin, can be so adjusted that a parallelism of effects and proportionality of work done can be shown to exist between these two ferments. If the same logic were applied to these phenomena as Pawlow and Parastschuk apply to milk-curdling and proteolysis, it would be equally possible to assert the amylolysis and proteolysis are due to one and the same enzyme, if it were not positively known that two definite enzymes were employed.

The method employed in Pawlow's laboratory to determine the degree of amylolysis is similar to that of Mett for proteolysis. Mett tubes are employed which are filled with filtered egg albumin coagulated in a water bath, and sealed at both ends with sealing wax. For amylolysis the tubes are filled with boiled starch in a similar manner. The diastasic power is expressed by the number of millimeters of boiled starch digested in a given time.

One of the most interesting facts discoverable during persistent analyses of human gastric juices is the total absence in some of them of the milk-curdling enzyme, while at the same time the peptic or proteolytic enzyme is present. This is proved by the fact that while the filtrate from test meals, consisting of bread and water, will not curdle milk, it will give the biuret reaction after it is added to discs of boiled egg albumin or to fibrin. This occurs in certain stages of chronic atrophic gastritis, when the milk-curdling enzyme disappears before the peptic enzyme. I have also seen it in two cases of cancer of the stomach. I must emphasize, however, that I have studied the gastric juice of two persons who are normal to all subjective and objective examinations. Into the stomach of one of these persons I poured a pint of milk, and withdrawing it by the stomach tube an hour thereafter it was in the identical condition in

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11. *Unters. a. d. Physiol. Institut der Universität Heidelberg*, vol. 1, p. 222.

EXPERIMENTS WITH DOG SALIVA AND TRYPSIN (PANCREATIC JUICE),  
DEMONSTRATING EFFECTS OF INCREASE OF TEMPERATURE, ON  
DIGESTION OF BOILED STARCH AND ALBUMIN  
RESPECTIVELY.

Canine saliva and trypsin solutions were subjected in different and separate portions to the various temperatures stated in column 1, and thereafter their amylolytic and proteolytic power tested.

Temperature. Deg. C.	SALIVA.	PANCREATIC JUICE—TRYPSIN.
	Mm. of Boiled Starch Column Digested.	Mm. of Albumin Column Digested.
10	4.20	5.52
12	4.15	5.5
15	4.25	5.9
20	4.25	6.
30	5.1	6.5
40	4.95	5.9
50	3.5	4.5
52	2.75	3.62
54	2.	3.
56	0.5	0.9
58	0.3	0.5
60	0.	0.
62	0.	0.
64	0.	0.

Both enzymes exhibit at first a slight increase of their characteristic effects followed by a gradual diminution until the enzymes are completely destroyed at 60° C., a parallelism of effects—which can also be demonstrated if both saliva and trypsin solution are poured together and a starch, as well as an albumin tubule, placed in the combined solution simultaneously. But here the action of amylopsin requires exclusion.

TESTS FOR ANY CHANGE OF ACIDITY VALUES IN THE GASTRIC JUICE  
ON STANDING AT ROOM TEMPERATURE.

Comparisons of work done by pepsin and chymozin of human gastric juices, together with quantitative determination of the free HCl and the total acidity. Gastric filtrates allowed to stand at room temperature for varying periods.

Notes.—1. Same gastric juice of Spencer when left in incubator at 36° C. began to lose its proteolytic power in 20 days. The milk-curdling power diminished more rapidly and disappeared entirely on the eighteenth day.

2. From Spencer a very large test meal was drawn, amounting to 780 cubic centimeters of gastric chyme, which was kept under experimentation 56 days.

3. In this table the figures show the proteolysis to diminish gradually from 8 mm. on January 3, to 4 mm. on February 23, but the milk-coagulating power diminishes much more rapidly and out of all proportion to the rate in which the proteolytic power diminishes. No parallelism in the diminution of these effects is here detectable.

WEINBERG.	November.					
Date . . . . .	17	18	19	21	22	23
Free HCl. . . . .	39	42	44	42	42	41
Total Acid. . . . .	62	64	63	65	56	70
Proteolysis in terms of millimeters of Mett albumin tubes.	4.5	4	4.5	4	4.5	4
Chymozin: 10 c.c. milk coagulated in minutes.	3'	3'30"	3'	3'	3'30"	3'



CARTRIDGE.	January.									
Date. . . . .	17	18	20	23	25	26	28	30	31	
Free HCl. . . . .	74	76	76	74	74	76	72	78	74	
Total acidity. . . . .	100	104	108	104	104	104	102	106	106	
Proteolysis in terms of millimeters of Mett albumin tubes.	8	8	8	8	8	8.5	7	7.5	6	
Chymozin: 10 c.c. milk coagulated minutes.*										

HAMILTON.	Dec.	January.									
Date. . . . .	30	3	5	7	10	12	14	18	20	22	26
Free HCl. . . . .	65	60	64	66	70	62	64	68	70	66	68
Total acidity. . . . .	110	110	116	120	124	120	118	118	120	118	118
Proteolysis in terms of millimeters of Mett albumin tubes.	6.5	6	6.5	6.5	7	6	6	6.5	7	6.5	6.5
Chymozin: 10 c.c. milk coagulated in minutes.*	4'	4'10"	4'	4'	3'10"	3'40"	3'40"	3'45"	3'10"	4'	4'

\*Increasing cloudiness of gastric filtrate made the exact time of turning of the dimethyl amido benzol more difficult to recognize as the filtrate became older.

DAWKINS.	January.				February.						
Date . . . . .	25	28	30		1	4	7	8	10	14	18
Free HCl. . . . .	60	62	62		62	62	60	60	62	62	62
Total acidity. . . . .	90	100	88		88	98	96	100	110	105	100
Proteolysis in terms of millimeters of Mett albumin tubes.	5	4	5		4.5	4.5	5	5	5	5	5
Chymozin: 10 c.c. milk coagulated by 2 c.c. gastric filtrate in minutes.	1'	1'	1'5"		1'5"	1'5"	1'5"	1'5"	1'5"	1'5"	1'5"

WARNER.	February.										
Date. . . . .	1	2	4	6	8	10	14	16	20	21	24
Free HCl. . . . .	26	24	24	26	26	26	28	26	28	26	28
Total acidity. . . . .	66	70	72	74	72	72	72	70	70	68	70
Proteolysis in terms of millimeters of Mett albumin tubes.	3	3	3	3	3	3	3.5	3.5	3	3.5	3.5
Chymozin: 10 c.c. milk coagulated in minutes.	5'	5'	5'	5'	5'	5'	8'30"	10'15"	10'5"	11'	12'15'10"

SPENCER.	February.										
Date. . . . .	1	3	6	10	14	16	18	20	22	24	28
Free HCl. . . . .	60	59	59	58	57	55	50	50	48	48	46
Total acidity. . . . .	65	66	66.5	67	68	67.5	68	69	70	72	74
Proteolysis in millimeters of Mett Albumin tubes.	6	5.5	5	5	5	5	4.5	4.5	4	4	4
Chymozin: 5 c.c. sterile milk coagulated by .2 c.c. gastric filtrate in minutes.	1'0"	1'2"	1'2"	2'0"	3'5"	3'5"	4'0"	5'5"	10'	12'5"	20'5"

WARD.	November.												December.			
	16	17	18	19	21	22	23	24	25	26	28	29	30	1	2	3
Date . . . . .	34	31	34	34	32	32	34	32	32	32	34	32	32	31	32	32
Free HCl. . . . .	48	47	48	48	48	48	48	50	50	50	49	48	50	48	48	49
Total acid. . . . .	5	5	5	5	5	5	5	5	4.5	4.5	5	4.5	4.5	4	3.5	3.5
Proteolysis in terms of millimeters of Mett albumin tubes.	3'15"	3'15"	3'15"	3'15"	3'15"	3'15"	3'15"	3'10"	3'20"	3'20"	3'24"	5'	5'	8'	6'	8'
Chymozin in 10 c.c. milk coagulated by 0.2 c.c. gastric filtrate in minutes.																

PYLE.	November.												December.			
	22	24	25	1	2	3	4	5	6	7	8	9	10			
Date . . . . .	29	29	30	30	31	30	31	30	31	30	31	31	31	31	32	32
Free HCl. . . . .	64	64	66	65	65	61	65	66	64	65	64	61	64	64	64	64
Total Acid. . . . .	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	5.5	5.5	5.5	5.5	5	5.5	5
Proteolysis in terms of millimeters of Mett albumin tubes.	3'30"	3'30"	3'50"	3'50"	3'50"	3'50"	3'50"	3'50"	3'20"	3'20"	3'20"	3'20"	3'20"	3'20"	3'20"	3'20"
Chymozin: 10 c.c. milk coagulated in minutes!																

SPENCER.	January.																
	3	4	5	6	7	9	12	14	15	18	20	21	24	26	28	30	31
Date. . . . .	60	60	60	60	60	60	61	60	61	61	66	65	65	65	65	60	59
Free HCl. . . . .	64	66	64	66	66	64	65	65	66	65	60	60	59	59	60	65	65
Total acidity. . . . .	8	8	8	8.5	8	8	8	8	8	8	8.5	8	8	7.5	7.5	7.5	7.5
Proteolysis in terms of millimeters of Mett albumin tubes.	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	30"	18"	18"
Chymozin: 5 c.c. sterile milk coagulated by .2 c.c. gastric filtrate in minutes.																	

which it was poured down through the stomach tube. Nor did this milk coagulate after it was allowed to stand in an incubator for three hours. Nor could it be made to coagulate by the addition of varying amounts of calcium carbonate, nor by the addition of 1/10 normal solution of HCl added until the normal amount which should be present in the gastric juice was reached. Milk to which HCl is added in this manner will coagulate when no enzyme is present, but it takes a much longer time. Gastric juice which was boiled, and thus had its enzymes destroyed, did not coagulate milk any

sooner than a solution of HCl of the same strength. In testing milk coagulation on the addition of HCl, the time in which the coagulation occurs is an important factor in the determination.

The same persons whose gastric juice could not curdle milk produced a feeble proteolytic enzyme, for the filtrate from an Ewald test meal gave the biuret reaction. This conclusion is based on the assumption that the biuret reaction is an indication of the presence of peptones. These gastric juices, although they contain no free HCl, to the ordinary color test showed a feeble dissociation of methyl acetate by the Hoffman-Ostwald method of determining the free HCl. This probably indicates that the HCl may be so loosely combined with proteoses and acid albumin that it can readily dissociate and in the presence of pepsin produce peptones, though the ordinary color tests (Congo red, tropeolin (00) phloroglucinvanillin) are negative.

We had in these persons a demonstration of gastric juices: (1) That contained no free HCl, but combined HCl because they were capable of dissociating methyl acetate only slightly; but could form acid albumin and hemopeptone; (2) that could not coagulate milk; (3) that gave the biuret reaction with an Ewald test meal. The conclusion seems justifiable that pepsin was present, but rennin or chymozin was absent, a conclusion which is difficult to harmonize with the view of Pawlow that the proteolytic and the milk-curdling effects are due to one and the same molecule.

As a further evidence of the differences between the chymosin of various mammalia, it should be stated that an antichymosin prepared by injecting the chymosin of the calf's stomach is not an antichymosin for the dog's milk-curdling enzyme. And, furthermore, an antichymosin (antilab) is not at the same time an antipepsin, that is, it does not arrest the proteolytic effect of the pepsin made from the stomach of the same animal from which the chymosin was prepared. If pepsin and chymosin (proteolytic and milk-curdling effects) were properties of the same molecule an antichymosin ought to be at the same time an antipepsin.

In their original article Pawlow and Parastschuk state that in their opinion chymosin acts synthetically, i. e., milk coagulation is the first stage toward the upbuilding of the new (native) proteid molecule; with this hypothe-

sis they aim to bring their views in harmony with the modern idea of the reversible action of enzymes (Kastle and Lowenhardt). Their viewpoint then is this: Pepsin and rennin (or chymosin) represent the same enzyme molecule—only pepsin acts analytically. Rennin (or the effect we attribute to the hitherto supposed rennin) is the evidence of the synthetic effect. Recently,<sup>12</sup> however Ernst Laqueur<sup>13</sup> has given the experimental evidence that chymosin or rennin acts analytically—i. e., splitting off a part of the casein molecule.

To Dr. R. A. Warner and Dr. J. Howard Iglehart, my associates, I am indebted for control analyses and tests in arranging above tables.

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12. This highly important insertion was made possible by the arrival of the journal quoted while the proof of this article was being read.

13. Hofmeister's Beitr. z. chem. Physiologie u. Path., vol. vii., p. 273; also Blochem. Centralblatt, vol. iv., p. 333.





PRESENTATION OF OIL PORTRAIT OF HIMSELF TO PROF. JOHN C. HEMMETER BY HIS FRIENDS, WITH ADDRESSES MADE ON THAT OCCASION.

On November 15, at his residence in this city, an oil portrait of Prof. John C. Hemmeter was presented to him by his colleagues and former pupils. The committee in charge were: Drs. Warner Holt, of Washington, D. C.; J. C. McAfee, of Macon, Ga., and Carl Nelson Brandt, of Hot Springs, Va. The occasion marked the twentieth anniversary of the doctorate of Prof. Hemmeter. A number of physicians and friends from Baltimore and other cities assembled at Prof. Hemmeter's residence, where the exercises were conducted, followed by a collation.

The BULLETIN is fortunate in being able to publish these addresses in full. The presentation address was made by Surgeon-General Walter Wyman, of the United States Marine Hospital Service, as follows:

*Dr. Hemmeter:* 1

I deem myself fortunate in having been selected by your friends to present to you this fine portrait in oil, commemorative of the twentieth anniversary of your doctorate.

These occasions are all too rare, when the intellectual and emotional parts of our nature are brought out together—the intellectual in the background and the foreground filled with expressions from the heart.

It is a delight occasionally to throw aside all thought of professional cares and official duties and give free exercise to our more natural sentiments of friendship and good fellowship. Too often the doctor is considered but a human being, somewhat set apart from the rest of mankind and devoted solely to his science. This in my early days was drilled into me as to what a doctor should be. I resented it then, and now as one of the elders I feel free to protest against it.

There is nothing in the medical profession which can claim from its devotees a sundering of those ties which bind all human beings in their social relations; nothing that should prevent the exercise of civic duties and an interest in all sciences, literature and art. 2

These are the ideas which are prompted by your own personality, for you have demonstrated in your life the great truth that a man may be a great physician, yet eminent in other walks of life, meeting the social demands of his nature, loving melody, and cultivating to a high degree a love of the beautiful and good as well as the true. Therefore, appreciation of intellect and appreciation of broad manhood alike have prompted this testimonial to you from your friends. 3

For your professional achievements we have the highest appreciation, and in this we are not alone. Eminent authorities in this and other lands have spoken eloquently of your published works; authorities and clinicians of international repute, as Ewald and Boas, von Leiden of Berlin, and Nothnagel of Vienna, have spoken for us, and rank the results of your work among those of classical medical scholarship.

With these few words, I present you in behalf of your friends this life-size portrait of yourself, in the prime of manhood; and as you and others look upon it, you and they will see not only the form of manhood, the impress of thought and character in the face, but in the frame which surrounds it there will be seen leaves of ivy signifying triumphs in science and art, and faces of friends beaming with pleasure on one who has endeared himself to his friends by his noble qualities of head and heart.

Dr. Warner Holt, chairman of the committee, made the following remarks: 3

*Dr. Hemmeter:*

It has been a great pleasure to the committee, and especially myself, to have been able to participate in the work of this evening, and to unite in one expression the sentiments of your many

professional admirers throughout the United States. 4

It has been our effort to gather in this testimonial, not only your own former and post-graduate pupils, but representative clinicians in other cities; and made no appeal to your confreres in Baltimore, except when a request to that effect was received. We in other cities look upon this testimonial as an indication that the University of Maryland has taken a position among the leading institutions of medical learning in the country (being free from that bias which may develop from too close a sectional attrition), having produced such leaders in medical research as Councilman, A. C. Abbott, William T. Howard, Jr., Hemmeter, and many others, and has had at all times some of the most effective clinicians and surgeons in its faculty.

The fame of the Alma Mater is inseparably connected with and even depends upon the character of the work of its alumni. And in this connection we delight in the words which Nothnagel wrote to the publishers of Dr. Hemmeter's works: "They are the products of a master clinician—an inspiring teacher—an ornament to American medicine."

Apropos to this event, it would seem a graceful act to make some reference, in a general way, to the influence of the University of Maryland on American medicine.

The University of Maryland was founded in 1807—an epoch-making period in American history. The lights and fires in this temple of learning have modestly illumined the shadowland of medicine and blazed the path, throughout her successful career, with wise conservatism in policy and educational methods. The history of every science attests conclusions having been revised and re-revised to more nearly correspond with realities. In fine, the progress of knowledge consists in marshaling Thoughts into harmony with Things. 3

In this respect the University of Maryland has often been first—and always among the first—in the adoption of measures and methods in

medical instruction, presaging the most fruitful results, as contributory factors in the process of high medical culture. She can point with pardonable pride to the many illustrious names among her alumni who have graced American medicine and surgery with emulable distinction and enduring lustre.

It seems as each expiring savant let slip the lighted torch from tired hands to become a star of destiny in the Æsculapian constellation, another valorous votary seized the heritage and bore it aloft in this unbroken column of truth-seekers. To-day, you will find them on the teaching staffs and in the laboratories of numerous medical institutions, delving in the mine of experimental facts—bacteriologic and biochemic—which submerge us, assaying the true from the false and minting them into accepted truths fit for the architecture of constructive medicine, dedicated to the physical and mental betterment of mankind. C

This University, in common with other great medical institutions, has, no doubt, her quota of alumni who have, like Atalanta, stooped to take up the golden apples, thus inhibiting the race in the prosecution and progress of medical science. It would indeed be difficult to measure and estimate the lasting impress and far reaching results made by the University of Maryland on American medicine. The achievements of her sons in the past and in the present form her obelisk. Her alumni are men who not only make history, but who are history. You will not find their names in "The Hall of Fame for Great Americans," as no scientist, physician, or surgeon has been impaneled therein. Their Hall of Fame is in the hearts of the American people. The world is influenced by the dead as well as by the living. In the language of Darwin—"Our lives are but a bundle of consequences; our present is but the outcome of the past." 'Tis here, on this occasion, that Past and Present touch—the nuptial of night and noon; the memorial in marble saluting the panegyric in painting. X

SCIENCE AND ART IN MEDICINE.  
THEIR INFLUENCE ON THE DEVELOPMENT OF MEDICAL  
THINKING.\*

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IS MEDICINE A SCIENCE OR AN ART?

Medical men the world over frequently have to hear the criticism, I might call it the reproach, that medicine is not a pure science, that its methods and its discipline are not sufficiently accurate to merit this term. On the other hand, critics are not wanting among the non-medical public, who argue that medicine is not a perfect art.

Now, what is an art, and what is a science? In a recent address President Ira Remsen<sup>1</sup> attempts to define these terms, and on the authorities there quoted by this versatile educator we might profitably start out by borrowing the interpretations of the terms science and art. One writer says: "The distinction between science and art is that science is a body of principles and deductions to explain the nature of some matter, and art is a body of precepts with practical skill for the completion of some work. Science teaches us to know, and art to do. In art, truth is a means to an end, in science it is the only end. Hence, the practical arts are not to be classed among the sciences." Another writer says: "Science and art may be said to be investigations of truth, but one, science, inquires for the sake of knowledge, the other, art, for the sake of production. Hence, science is more concerned with the higher

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\* Address on occasion of conferring of the degree of doctor of laws (*honoris causa*), St. Johns College, Maryland.

1. "The Age of Science," *Science*, July 15, 1904.



truths, and art with the lower. Science is never engaged, as art is, in productive application."

These definitions are apparently not equally clear with regard to science and art. With regard to science, they are clearer than with regard to art. Science has for its object the accumulation and systematization of knowledge, the discovery of truth. This part is clear, and also that art is a body of precepts with practical skill for the completion of some work. But it is not clear how truth is only a means to an end in art, and in science it is the only end. Surely, if a truth could be expressed as a precept in as concrete a form in any art as it could be in a pure science, it would be, or at any rate should be, the only end, the only object of the art as well as of the science.

Then the question might arise, What are higher and what are lower truths? In the decision much depends on the individual standpoint of the judge. What is a higher truth for a scientist may be a lower truth for an artist, and *vice versa*. If it is said that in art truth is a means to an end, we have a right to inquire what is meant by the truths of an art? For instance, are counterpoint, thorough base, and harmony the truths of music?

I know of but two individuals in the history of the modern scientific world who, by training and experience, could be considered competent to answer this question, both having been artists and scientists at the same time, of acknowledged ability. One was Hermann von Helmholtz, physicist, physiologist and musician. The other was Theodor von Billroth, anatomist, pathologist, surgeon and musician. Both of these men have given us the benefit of their thinking on the borderland between science and art. Helmholtz, in his "Sensations of Tone," and Billroth, in his "Psychologische Aphorismen über die Musik" (Wer ist Musikalisch). To the student of either of these works seeking information on the questions above propounded, it must soon become evident that an exact and definite distinction between art and science is not always possible; particularly it is not possible in any concrete case. We are, therefore, enabled to meet the critics arguing that medicine is not an exact science nor a perfect art, with the statement that a distinction between these two is by no means possible and that there is much debatable territory between

human knowledge and human ability. Medicine did not originate as a science, but by dire force of necessity. For centuries on centuries its treasures were gathered from experience only, and were developed into an art by the genius of its representatives. Professor Remsen<sup>1</sup> was, perhaps, too accurate in attempting to draw a hard and fast line between art and science. Every science is desirous to become an art, and every art tends to become a science. So also medicine. I mean by this that art requires a scientific foundation and that science requires ability to do. In other words, science requires productive application, the power of achievement.

My convictions induce me to differ from my erudite teacher, Professor Remsen. At least, to differ with him in applying the same ideas to medical science as he is disposed to set up for the science of chemistry. In rating the history of the discovery of oxygen and chlorine by Scheele (1774), he lays great stress on what seems to him a fact, that Scheele did not work toward these discoveries with any practical object in view, and, though this work, while it was being done, seemed to be of no utilitarian promise, its value in the light of present-day industry can not be overestimated. It would be very difficult to prove that Scheele worked absolutely oblivious of any practical results that his work might have. It is true that scientific men frequently work from pure love of science, prompted by high ideals and disinterested enthusiasm, but there is often an undercurrent of thought which is sometimes discovered in the private correspondence of chemists, that the work they are doing may yet be of utility to their fellow-men, and perhaps profitable to themselves. In medicine, too, we have the history of a large number of unselfish workers. But if they should work purely in following ideals, without any hope of gaining any utilitarian results, they are not medical men in the true sense of the word. Medical science shall and must be useful. A quotation from Cicero is well applicable here: "*Nisi utile est, quod faciamus, stulta est gloria.*" An oft-quoted saying of Bismarck is: "*Die Politik kann nicht im Laboratorium gemacht werden, denn sie hat überall mit dem Menschen zu thun.*" (Politics can not be made in the laboratory; they have everywhere and at all times to deal with the human being.) In an analogous manner

one may say of medicine: "Medical science can not be made exclusively in the laboratory; it has always and everywhere to deal with human beings." I said medical science, but I would, perhaps, have been more exact to have said medical art. For science analyzes, it dismembers and disintegrates in order to penetrate into the depths of things, and to study the final microscopic living element, the cell, in its life properties and processes. This is true, for instance, of physiology and anatomy. But art in medicine keeps the whole together, it observes the individual, the human being, in its entirety. Science seeks general laws; art in medicine seeks the personality. The object of all medical science is to help and to heal, and the object of all medical, artistic and scientific thinking is the therapeutic thinking. Scientific facts in medicine may have an absolute value, although they may not be directly useful, but, aside from such an absolute value, the whole art and science for the physician must be concentrated on the desire to aid his patient in regaining health by means of his science and art. Prof. I. Peterson, of Copenhagen, was one of the first to assert: "The attempt to erect the medical clinic exclusively on the achievements of natural science has proven itself to be impossible of execution."

#### HISTORY OF MEDICINE.

The evolution of medical thinking can best be studied in the history of medicine. From the earliest rudiments among the Egyptians, Romans and Greeks, the first beginning of clinical discipline dates from the Arabic apostles of medicine and the religious medical thinking, which was the custom of the healing monks of the medieval ages, who were the founders of the schools of Salerno and Monte Cassino. A new period begins with Paracelsus, a man who was an excellent chemist for his time, a contemporary of Luther, and based his therapy on a chemical substratum. Paracelsus created the conception of the "*Archeus*," the central ruler of the human organism, which holds all the bodily functions together and regulates them. This idea occurred later in the writings of Georg Stahl, under the name of "*anima*," and even in our time is frequently met with in a disguised form, sometimes under the designation "vital force." Scientific thinking, that is, thinking based on observations of objective facts, began rather late in the history of medicine. Not until the founda-

tion of universities did it meet with appreciation and respect. This was brought about mainly by the great anatomists of Italy, particularly by Andreas Vesalius, a German by birth (Andreas Wesel), but professor in Padua, 1537 to 1544. Then followed Malpighi, Botalli, Harvey, the celebrated discoverer of the circulation of the blood, and eventually Morgagni (1682-1771), the founder of pathologic anatomy.

This brings us to a period in the history of German medicine in which this science began its emancipation from philosophic and purely deductive thinking, to the scientific and inductive method of investigation, including severe criticism and testing of facts by exact proofs and experimental research. At the time the battle began in Germany between philosophic and scientific thinking in medicine, the methods of the natural science had already gained victories in England and France, and a new era of logical scientific thinking had begun under Rokitansky and Skoda in Vienna, but the course of the struggle was most interesting in Germany, particularly in Berlin. It was begun by an intellectual giant of such rare genius and unfailing logic that he might be called the father of exact physiology and medicine in Germany. I speak of Johannes Müller. He was the first to compel the abandonment of the philosophic thinking in medicine, insisting on the methods of the natural sciences, on investigations based on exact facts, on tests by experiment, and on the importance of microscopic investigations. The work of this great master was continued and perfected by two great pupils, Hermann von Helmholtz and Rudolph Virchow. Helmholtz particularly condemned the effects of the volitional thinking of the medical philosophers of his day, accusing them of contempt for exact investigation of the facts. "Natural philosophy in medicine," he says, "aims to explain the phenomena of normal and abnormal life, from the idea of absolutism. It is working toward a false idea of science, in a narrow, incorrect and one-sided appreciation of the deductive methods. It is true it was not only medicine among the sciences which was ensnared in these errors, but in no other science were the evil consequences so evident and did they obstruct progress so effectively as in medicine. The history of medicine, therefore, can claim a very special interest in the history of the development of human thought, for no other



history is better adapted to demonstrate that a correct criticism of the sources of our knowledge is practically one of the most important duties of true philosophy." The demands of Helmholtz for exact scientific methods in medicine, when brought into practical execution, succeeded in raising our science to the standard of an exact discipline and brought it into possession of a wealth of solidly grounded facts.

The other great pupil of Johannes Müller, Rudolph Virchow, became the reformer of medicine in another direction. While professor in Würzburg, in 1849-1856, he laid the foundation of his cellular pathology, and later on, in 1856, when he was recalled to Berlin, he continued the work of his great teacher in perfecting the science of pathology and pathologic physiology, based on individual investigations, on experiment and on pathologic anatomy. The conception of a disease became an anatomic conception, through Virchow, but his pathologic anatomy aimed also to fathom the processes of the living body, and to become a beacon light for clinical study, and in that sense was a truly biologic science. For nearly half a century Virchow continued to be the undisputed chief and the greatest authority on the totality of medicine in the civilized world; and it is no exaggeration to say that no other scholar in the history of medicine has exerted a like influence on the thinking of the medical world. As von Leyden says: "He impressed the stamp of his intellect on his time."

This sketch will serve to represent the history of medical thought from the incipency of medicine as an art to the present day. We are now living in the era of the naturalistic, methodic and anatomic thinking in medicine. What influence has this had on the artistic side of our profession, the clinic?

#### MODERN CLINICAL METHODS.

It must be emphasized right here that at the time when Helmholtz and Virchow began to be active in Germany, the methods of the natural sciences had already taken root in Paris, Vienna and in England. During the time that pathologic anatomy found its propounders in Cruveilhier and Rokitansky in Paris and Vienna, respectively, and at the time in which the clinic of Paris was under the inspiration of Laënnec and the clinic of Vienna under Auenbrugger and Skoda, the German clinic was still dominated by the philosophic

medical thinking. von Leyden states that the language of the clinicians was Latin and that they followed the volitional deductive methods of Leibnitz, Kant and Hegel. The first clinicians were Reil, Berend and Bartels. Reil was a natural philosopher, and Bartels had been a teacher of anatomy in Hildesheim, while the best that could be said of Berend was that he was a "thorough connoisseur of the writings of Hippocrates." Hufeland, a clinician of genius and influence, who followed these men, showed "*Wes Geistes Kind*" he was by corresponding with the philosopher Kant on his work concerning "Makrobiotik," and expressed himself disparagingly concerning the new diagnostic methods of auscultation and percussion.

But, in 1844, a contemporary of Johannes Müller was called to Berlin, and to this clinician, Lucas Schönlein, is due the credit of having replaced the Latin by the German language in clinical teaching. He brought about the appointment of the very able younger clinicians, H. Simon, Remak and L. Traube. With these men began the methods of exact physical examination of patients. Traube particularly was a master of diagnostic methods.

But when we look to the development of internal therapeutics at this stage of advanced clinical methods in Germany, it is discovered that the attempt to base therapeutics on pathology and diagnosis had failed. Therapeutic nihilism prevailed at Vienna, and the best that could be said of Berlin was that it worshipped the expectant plans of treatment. It took many years to impress on the clinician what now seems to be acknowledged a self-evident fact, that the only object of medicine is to help and to heal, and after the highly interesting evolution of the purely scientific part of medicine, briefly outlined in the preceding sketch, reformers were needed to emphasize again and again that, in addition to a science, medicine was also an art. Peter Krukenberg, a distinguished clinician of Halle, stated this in the following words: "Medical treatment, that is, therapeutics, is and will always remain an art." This conception of the clinical duties and responsibilities of medicine has been designated by Prof. I. Peterson<sup>2</sup> as "modern Hippocratism." The ultimate object of all medical studying is to help and to heal. The peculiar

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2. Verhandl. d. Congres f. i. Medicin, 1899.

problem of the physician is not so much the disease, but the diseased patient; and the significance and importance of medicine is to be sought in this object, to protect the highest possessions of human beings, namely, life and health.

#### RECENT ADVANCES IN MEDICAL ART.

A brief résumé of the advances in the art of applied methods of healing will give some idea of the progress that has been made in our art during the last two decades. I will begin with three methods of discipline not as a rule classed among the applied therapeutics in the ordinary sense of the term. I mean, first, the physical methods of treatment; secondly, the treatment by diet, and, thirdly, the treatment by the art of nursing and the direct attention to the comfort of the sick.

Concerning the physical methods of treatment, I may say that, while they are by no means new, they have received such admirable and utilitarian additions and developments that modern physical methods of treatment almost constitute a new branch of applied therapeutics. The treatment by baths and water in general, balneology and hydrotherapy, the treatment by exercise and special apparatus for the correction and passive and active motion of diseased muscles, joints and bones, by gymnastics and massage. The wealth of methods by which electricity can be applied, and photo- as well as heliotherapy, the therapeutic applications of different kinds of light, has been endowed with such an abundance of new apparatus and methods that almost each one of them requires a specialist for their perfect application.

The treatment by diet has been placed on the safe and sound foundation of the physiology of nutrition. It has been aptly designated by von Leyden "Ernährungs-Therapie." Not only the selection of the quality and quantity of the food, but the manner of its preparation, the cooking, has received attention of medical men, particularly those whose attention is concentrated on diseases of metabolism and of the digestive organs. There are probably few healing methods by which more permanent good can be accomplished in the diseases just mentioned than by a scientific method of dietetic principles. It is much to be regretted that the art of cooking has not yet been universally admitted as an integral part of the curriculum in schools for girls and young ladies. It is unfortunate that in our well-to-do and

even in the middle classes cooking is considered a humiliating occupation, a thing in which the modern housewife takes but a very superficial interest, leaving it, in the great majority of cases, to the cook whose experience and ability is a very variable quantity. The health of our people depends largely on the products of the kitchen, and the work of the kitchen is just as ennobling and honorable as any other work in any other walk of life. Cooking should be taught in every nurses' training school; and this brings me to speak of the art of nursing, the direct and immediate service toward the comfort of the sick patient.

Nursing constitutes the ethical factor in the vocation of the physician. It is that part of the applied art of medicine which gives it the character of devotion to suffering humanity, and which invests the physician with the reputation of sympathy and love for his fellow-men and women. Nursing is that branch of applied therapeutics in which our sisters, wives and mothers can join hands with the physician. It is individual and personal, it is the tie which binds the personality and individuality of the physician with that of the patient. Attention to the comfort of the patient and efforts at the widest application of the art of nursing afford also a common ground for two other much to be desired objects of our art: first, to secure for it the greatest possible support from philanthropic individuals and from the state and nation, and, secondly, to unite the more and more digressive specialties in medicine on the common ground of relief to human suffering. Here we have a tendency in which our claims for philanthropic and state support find a real and enduring sentiment and justification. For we can not claim this support for medicine as a science alone, but we can claim it for medicine as an art. For it is not exclusively the sciences which secure the blessings to the vocation of the physician, but it is the devotion to the relief of suffering, the readiness to help, the sympathy and the kindness of heart.

Right here a word of caution will not be amiss in reference to the ultrabacteriologic doctrines of the causation of disease and their influence on the treatment of the sick. This caution has already been expressed by Prof. O. Rosenbach, of Berlin, viz., we must not let any possible fear of contagion convert our sympathy and



love for the patient into fear of the patient. It can not be denied that from time to time a physician or a nurse may contract a disease from the patient. There is no doubt in my mind, however, that for every one of such cases of direct infection there are ten others in which nurses and physicians have actually been protected from the disease by virtue of their very intercourse with the patient. According to the ingenious theory of Ehrlich, very slight infection, sometimes scarcely noticeable by symptoms, may actually immunize an individual against a severe attack of that disease. It has been known to me, for instance, that a family in which there was a typical case of typhoid fever, the blood of the remaining members of the family gave the Widal reaction, yet to all appearances they were in a perfectly healthy condition. The antibodies were being produced in their circulation and tissue cells, preserving them from a severe attack of typhoid fever, not only for the time being, but doubtless for a long time to come, and all this without even getting sick. Therefore, such experiences have led me to agree with Rosenbach in the opinion that intercourse with patients suffering with infectious diseases, especially with light attacks, may be able to protect and immunize the nurse and physician against infection. This does not by any means signify that the ordinary precautions against infection can be thrown to the winds. It is mentioned merely to strengthen the nurse in her devotion to duty and to avoid thwarting of her efforts by fear of contagion.

#### RECENT PHARMACOLOGY.

After the physical methods of treatment which I have mentioned, those offered by pharmacology rank next in importance. The products of the pharmacist and physiologic chemist have much enriched the armamentarium of the physician. Many new antipyretics have been brought out, medicines have been manufactured in a purer form, and older medicaments of approved value have been changed to a more pleasant form. New and useful medicaments for the production of sleep and the lessening of pain have been brought out. I greet it as a specially valuable advance that several remedies for the relief of pain, which hitherto could only be taken internally, and though very useful for the disease under treatment, yet frequently disarranged the digestive apparatus, can now be effectively administered externally

through the skin. It has thus been found that very effective preparations of salicylic acid can be brought into a form which, when brought on the skin, will be so rapidly absorbed that the reaction for salicyluric acid can be discovered in the urine within half an hour of the external application. The art of general and local anesthesia has experienced wonderful improvements in apparatus, technique and combination of agents.

Bacteriology has not only brought fertile ideas and facts into the science of pathology, but has opened an inexhaustible field for therapeutics. The discovery of the cure for hydrophobia and anthrax by Louis Pasteur and the discovery of tuberculin by Koch was soon followed by the antitoxin serum for diphtheria and tetanus by von Behring. In connection with these glorious achievements, serum-therapy began to develop as one of the methods of applied therapeutics. It is true that of the many serums thus far prepared only that for diphtheria and that for tetanus have proved generally useful. The fact that the cholera, plague, typhoid, scarlatina, antistreptococcus and rheumatic serums have so far not proved as effective as those previously mentioned need not discourage further efforts to perfect them.

The explanation of the difficulties of preparing effective serums is given by Paul Ehrlich in his ingenious theory on immunity which has brought the complicated phenomena of immunity nearer to our understanding. The study of the effect of bacteria on the human organism has led to the discovery of the protective substances of the blood, of the toxins and antitoxins, of agglutinins and precipitins, of the cytolytic substances. It is impossible here to enter on the consideration of that most wonderful and stimulating of modern medical hypotheses on immunity which has been developed by the genius of Ehrlich.<sup>3</sup>

I desire to call attention to a probable outcome of these studies on immunity, to which I have elsewhere referred<sup>4</sup> concerning the rôle of intracellular catalytic processes in the pathogenesis of malignant neoplasms.

3. Aschoff, Ehrlich's Seitenkettentheorie, etc., *Zeitschr. f. Allgemeine Physiologie*, vol. 1, No. 3, 1902; also Wm. H. Welch, the Huxley Lectures on Immunity, *Science*, Nov. 21 and 28, 1902; and A Résumé of Recent Researches Relating to Immunity, by T. Mitchell Prudden, *N. Y. Med. Record*, Feb. 14, 1903.

4. *Amer. Jour. of Med. Sci.*, April, 1903

If it be possible so to adapt the blood of an animal to a particular form of cell that its serum shall become specifically destructive of these cells, we have here a possibility for the preparation of serums which will be effective in restricting the growth and perhaps of locally destroying malignant and other tumors. My own studies on the transplantation of malignant tumors lead me to believe that, with a fuller knowledge of cytolysis, the outlook for such serums will be more promising.

Closely associated to serum therapy is the treatment of disease by extract of animal organs, which is gaining more and more in definiteness and exactness of application. Perhaps the most interesting of these substances is the active principle of the adrenal bodies, epinephrin, first isolated by John Abel of Baltimore. Thyroidin and spermin belong to this class of remedies.

The astounding chemical versatility of the cells of the body, as evidenced in the production of such substances, and the immune bodies to which I have referred before, has forced on us a conception of the cell household as a complicated chemical laboratory. Prof. Franz Hofmeister, of Strassburg, in his essay, "Die Chemische Organization der Zelle," conceives the cell as executing its work by manifold enzymes, each working alone in a special little cell compartment. Thus we have a biochemical conception of the cell processes. This is analogous to the conception of Ehrlich, on which he has built his side-chain theory of immunity. Benedict, on the other hand, Jacques Loeb, and perhaps Wilhelm Ostwald of Leipzig, have developed the biomechanical conception of the cell's work. Virchow's conception was, in principle, a purely anatomic one. Thus we have many varied conceptions of the manner and means by which the cell performs its regular and irregular processes. Though apparently widely digressing, it is encouraging to observe how many of the more important of the results of the biochemical, biomechanic, and the purely anatomic methods of thinking, concerning the cell, are beginning to overlap and even to agree with each other.

#### SUBJECTIVE AND OBJECTIVE METHODS IN RESEARCH.

It might be argued that methods of thinking can not develop a science in themselves. This is true, for thinking should always be linked with observation and experiment. But, on the other hand, neither observation nor experiment alone can make a science. The forma-

tion of conceptions, however, from hardened facts of observation, and logical deductions of experiments, can form and develop a science. Unfortunately for our present methods of advancing medical knowledge, experiment alone has usurped the entire machinery of medical progress, and observation, as well as medical thinking, have been pushed to the background. It can not be sufficiently emphasized at the present time to use the words of Socrates, that "the conception is the fundamental condition of apperception and understanding," and Plato says of the sophists, "In the absence of a correct conception, they hold a learned discourse on the ass, when they mean the horse."

Very regrettable delays and even reverses in the progress of medicine have been experienced by the fact that one or other observer or investigator attempted to build his road into the unknown territory exclusively on one of the methods above outlined, namely, medical thinking, or observation, or experiment. One has criticized the value of thinking, the purely subjective method, another finds fault with the method of observation, a third applies his restrictions to the method of experiment, the purely objective method. This has resulted in an accumulation of a vast amount of scientific building blocks, but there is no coherent complete architecture in the modern science of medicine, and this is at least in part due to the perfectly unnatural separation of the three methods of attempting medical progress. It is very rare to find in modern medical literature even an attempt at a complete scientific plan, and this is largely explained by the fear of most investigators to use the method of medical thinking, or the subjective method, in association with the objective method. Martius (*Pathogenetische Grundgedanken*) says: "It is a curious thing that the more scientific, the more exact the method of an investigation in medicine, the more inimical to thinking are its advocates." This is, indeed, curious. Why should exactness of a method be associated with hostility to our subjective powers of research, the power of thinking, as a help for the solution of medical problems. Darwin, Hæckell, Julius Robert Mayer, and Helmholtz were not only great investigators, but even greater thinkers. The century that produced steam railroads and the electric light gave us the law of conservation of energy by Mayer, and this law, probably the greatest discovery of the nineteenth century, is pro-



claimed by those most competent to judge to be the fruit of a purely thinking act, and that the experiment attached thereto was a sequence to the thought. Investigators who pursue objective methods of research, based on experiment alone, pride themselves on their exactness in methods. Exactness and accuracy constitute, in the opinion of the experimentalist, the only and the most logical measures of correctness. But what is this exactness, the painful application of units of measurement, of units of weight, of instruments of precision, of accurately controlled conditions of arrangement in the experiment? What is all this exactness but the translation of a frequently very complicated act of thinking into manipulations of science? The thought preceded the experiment. The subjective preceded the objective method.

J. P. Pawlow,<sup>5</sup> most scholarly of Russian physiologists, attacks the adherents of vitalism and animism in physiology in a recent contribution. These terms, vitalism and animism, refer to the tendency to return to the older conceptions in physiology, which attributed the phenomena and processes of life to a "vital force," the "archeus" of Paracelsus and the "anima" of George Stahl, a something which was not explainable by the laws of chemistry or physics. The application of chemistry and physics to physiology has enabled us to understand a great many of the processes of life, and to explain them on a purely chemical or physical basis. But some of the clearest thinkers in physiology admit that many of the processes of life can not be explained on such a basis, and they begin to favor views attributing such life phenomena to a special energy in the living substance (neovitalism). They who favor the vitalistic and animistic aspects of physiology are apt to confuse the standpoint of the investigator of natural science with that of the philosopher. The objective investigator has hitherto accomplished his most far-reaching results by the study and comparison of objective facts, during which he ignored questions concerning the inner subjective nature and the fundamental principle underlying the thing investigated. The philosopher, however, embodies the tendency toward synthesis of thought, and in attempting this he begins by a fusion of objective and subjective

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5. "Psychische Erregung der Speicheldrüsen" (Ergebnisse d. Physiologie), 3d year, vol. I, p. 177.

phenomena. For the investigator everything depends on the objectivity of the method. This gives the possibility of finding solid and unbreakable facts and principles. This is the view of Pawlow. In my opinion, subjective and objective methods of investigation are inseparable. Even where the investigator believes himself to be purely objective in his methods, he is unconsciously and unavoidably subjective, because the objective accuracy and precision of his methods represent but a translation, an outward projection, of his own subjective train of thoughts, and when his objective facts are established they must again be linked and amalgamated into his own thinking, or that of others, in order to be of value for the progress of knowledge.

#### DIFFERENCE BETWEEN TRUTH AND FACTS.

We are living in a period in the history of medicine in which the experimental tendency has gained supremacy over speculative philosophy in medicine. But we are in the possession of such an enormous amount of new material and facts, which by additional experiments is daily increasing, that the new facts frequently must be allowed to remain unused, and are, for the time being, of no assistance in the advancement of our science. In this connection, I must again repeat what I have emphasized in the preface of the second volume of my work on "Diseases of the Intestines," namely, the difference between truth and mere facts. These two are often, unfortunately, considered synonymous. Facts are little truths that our senses are capable for the present of comprehending; but back of, and beyond these facts, later experience often reveals the higher and greater truth. An experimental fact which to-day seems absolutely disconnected and, therefore, without meaning may to-morrow, when viewed in another light, suddenly assume a far-reaching significance and importance. No new fact of experience or experiment, be it at present apparently ever so remote from practical bearing, need be considered worthless, provided it is correct. It may be allowed to rest as raw material for a time, but it is probable that in another association it may acquire an importance which we did not anticipate.

But this I must emphasize, that an isolated, disconnected fact of experience or experiment has, for the time being, no significance for the progress of medicine. This significance comes only, then, when we can arrange and

fix this fact into the already existing and firmly established architecture of our knowledge. There exists a danger in overrating the value of single facts of experience and experiment. Individual facts discovered this way are accumulating to such an extent that we are completely submerged under an ocean of experimental results, and the intellectual interpretation which fits them into the synthetic structure of our science is missing. Physicians who are not participants in experimental undertakings feel very painfully this absence of the connecting link between an enormous number of new acquisitions which, though experimental, are in a sense empiric. This is also true of the experimental acquisitions in bacteriologic as well as biochemic domains. In the eighteenth and during the first part of the nineteenth century medicine was comparable to a sterile unproductive heath, in which some evil spirits drove about the speculating medical philosophers in a circle. Now we have gotten into an overfruitful swamp or jungle in which the facts grow so luxuriantly that they threaten to smother our thinking powers. The tendency of all laboratories is to bring out new facts. Let us have all of them if it must be, but what we need as much, if not more than new facts, are master minds who will instruct us in the interpretation of these and old facts, and give them a meaning and value by fitting them into the synthetic structure of physiology and medicine. Martius compares modern medicine to a sense-confusing concert, and what is needed is a disciplinarian to instruct us concerning the leading motives, to seek the familiar law in the revealed wonders of the present time.

Aber im stillen Gemach entwirft bedeutende Zirkel  
Sinnend der Weise, beschleicht forschend den Schaffenden  
Geist,

Prüft der Stoffe Gewalt, der Magnete Hassen und Lieben,  
Folgt durch die Lüfte dem Klang, folgt durch der Aether dem  
Strahl

Sucht das vertraute Gesetz in des Zufalls grausenden Wundern,  
Sucht den Ruhenden Pol in der Erscheinungen Flucht.

—SCHILLER.



## THE ONE HUNDREDTH ANNIVERSARY OF THE UNIVERSITY OF MARYLAND.

BY JOHN C. HEMMETER, M.D., Ph.D., LL.D.

"VIRIBUS UNITIS." — "*With united forces,*" this must be the motto of all University of Maryland Alumni, Legal, Dental, Pharmacal, and Medical, and even of all undergraduate students in the vigorous preparation for the hundredth anniversary of our dear Alma Mater. Success can only be accomplished if all these forces pull together with the professors and regents; even the most modest student must feel it his duty to contribute something, and to the best of his ability. If he cannot contribute anything else, let him at least contribute his enthusiasm. The students of all classes of all departments should hold meetings during the month of March, and organize for the purpose of adding their small building blocks to the mighty festival structure which shall commemorate the centennial of the University of Maryland. The regents of the University of Maryland have appointed the following committee to have charge of all preparations for the festival:

W. Calvin Chestnut, LL.B.; Edgar H. Gans, LL.B.; John P. Poe, LL.D.; R. Dorsey Coale, Ph.D.; Charles W. Mitchell, M.A., M.D.; David R. M. Culbreth, Ph.G., M.D.; John C. Hemmeter, M.D., Ph.D., LL.D., Chairman.

On the 21st of February, Professor Hemmeter called a meeting of all the committees of all the elected, by the adjunct faculty, the Medical Alumni Association and the Alumni Associations of the other departments of the University to confer with the above committee concerning the best way to make befitting preparations for the celebration of the one hundredth anniversary of the University of Maryland. At that time the regents had decided that in strict accord with the history of the institution only the centennial of the MEDICAL department could be held in 1907.

By request of all the Alumni attending the meeting of February 21, the regents were induced to reconsider this matter, and on February 27 a very largely attended meeting of the regents met for this purpose, at the offices of Mr. John P. Poe. The following resolution was unanimously passed on that occasion:

### MEETING OF REGENTS OF THE UNIVERSITY OF MARYLAND, FEBRUARY 27, 1906.

*Dr. Hemmeter in the Chair, John P. Poe, Esq., Secretary.*

After an explanation of the object of the meeting by chairman, Professor Poe moved,

RESOLVED, *That it is the sense of the Regents in council assembled that, inasmuch as the School of Medicine, organized in 1807, was the foundation of the University of Maryland, by the annexation to it of other departments, a centennial celebration of the whole University may properly be held in the year 1907.*

This motion was unanimously carried. There is, therefore, no further doubt regarding the scope and extent of a festival to be held in May, 1907. It is to take in the entire University of Maryland. The medical regents, notwithstanding all reports to the contrary, were always, and with one accord, in favor of this view of the celebration. It was owing to an opinion given by the most prominent of regents of the Law department (Messrs. Bernard A. Carter, Edgar H. Gans, and John P. Poe) that the medical regents reluctantly gave up the hope of celebrating the event of 1907 as one comprising all departments of the University. Even at the last meeting of the regents Professor Poe expressed the opinion that the extension of the centennial idea to embrace all the departments of the University *was won by construction.*

Be that as it may, we need the help of all departments alike, especially of the law department and all of its Alumni. The alumni of the department of law should feel it their duty to aid in



this celebration, for it is also the hundredth anniversary of their University. Let us see how the legal brethren that have emanated from this institution will prove their loyalty to it. The sentiment of the faculty of medicine concerning the celebration is clearly portrayed in the address of welcome by Dr. Hemmeter on February 21, which was as follows:

*Fellow Alumni and Friends:*

The most pleasant duty in calling this meeting to order is to extend to you academic greeting. Be cordially welcomed and assured of the friendship of the regents of the Faculty of Physics.

This representative meeting is not a response to a general call to the Alumni, but only to special invitations sent to committees elected by the various faculties, the adjunct faculties and the various Alumni Associations. I hope we shall have a larger and general meeting in the near future as a result of a call to all Alumni that can reach the Alma Mater by a few hours' trip on the railroad. To the committee of our Washington Alumni Association—an ornament to this University and active factor in the progress of medical science at our National Capital—I desire to express a warm assurance of our joy at this manifestation of their loyalty.

Too seldom have these reunions been held at the hearth of our intellectual mother. *Let us recognize the beauty and power of true enthusiasm, and whatever we may conclude to do, for the purpose of celebrating the 100th Anniversary of our Alma Mater, let us guard against checking or chilling a single earnest sentiment.* A university is not an aggregate of buildings, but

of thinking men of human minds. And *what is the human mind*—however enriched with acquisitions or strengthened by exercise—when unaccompanied by an ardent and sensitive heart? Its light may illumine, but it cannot inspire. Knowledge without a heart may shed a cold and moonlight radiance upon the path of life—but it warms no mental flower into bloom, it sets forth no ice-bound fountains of conservatism. Dr. Johnson has often been quoted as saying that an obsolete rationality and conservatism prevented him from being a Papist. Does not the same cause prevent many of us from unburdening our hearts and breathing our devotions at the shrine of our Alma Mater—obstinate rationality and conservatism not only among the Alumni, but also among our regents and faculties? There are influences which environ humanity and all leading institutions which are too subtle for the dissecting knife of reason. Let us see whether we cannot make these influences a means of blessing to our present purposes. Let us be in our better moment clearly conscious of our loyalty to fellow-alumni and to the University, and if there is any barrier to sentiment and friendship, may God convert it into a blessing.

The object of this meeting is to make befitting preparation for the celebration of the 100th Anniversary of the University of Maryland.

The regents have determined to hold such a celebration in May, 1907, and they desire your advice and assistance for this purpose.

I cannot conceive of the conclusion of one century of glorious history and meritorious work and the entering upon a new one without the accomplishment of some great object to the advantage of the future of the University, and this should be a warmer, closer relation with the Alumni and the foundation of an Alumni professorship; that is the endowment of a professional chair by the Alumni and that be filled by vote of the Alumni.

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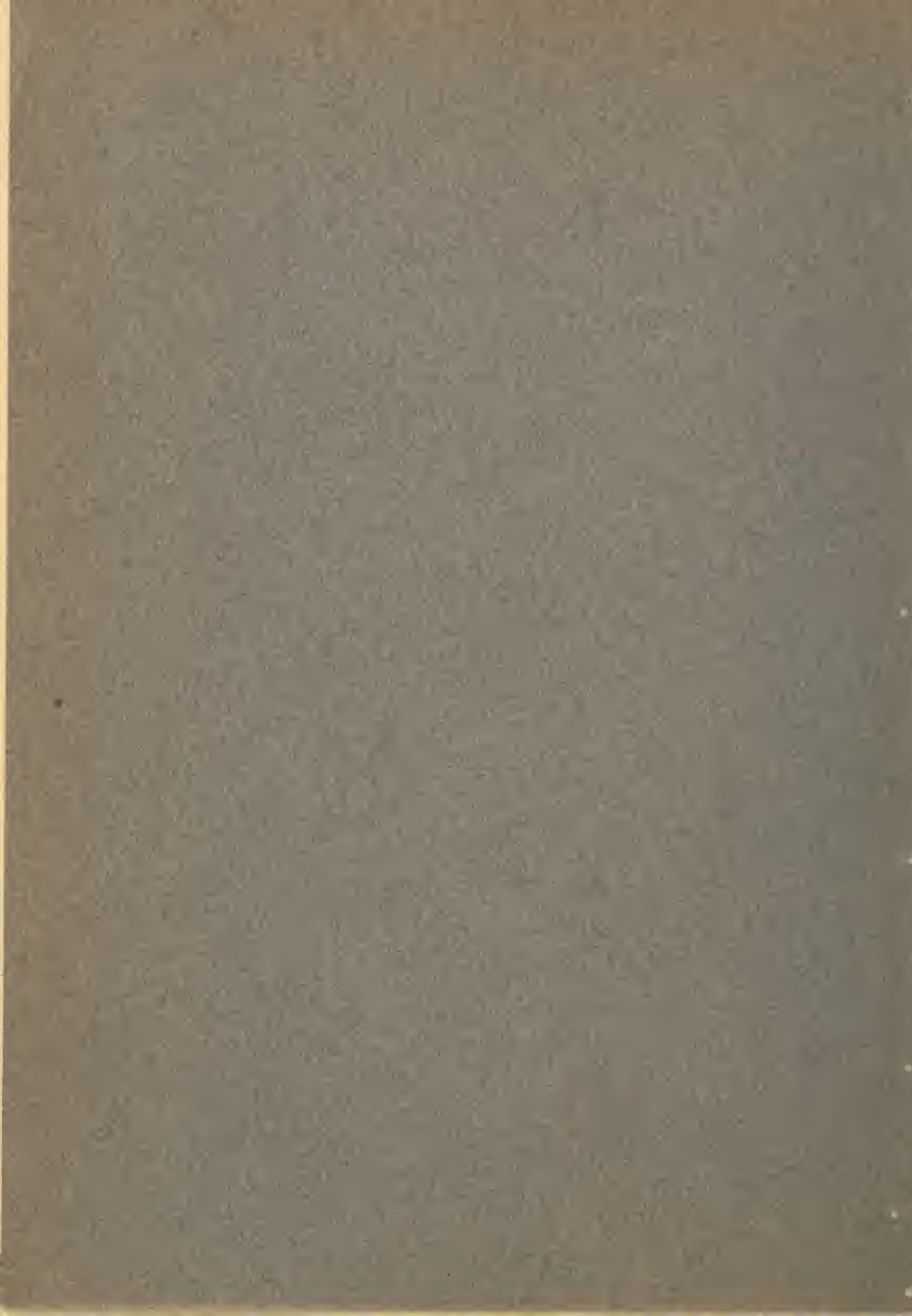
German-American Influence  
IN  
Medicine and Surgery

BY  
JOHN C. HEMMETER, M.D., Phil.D., LL.D.  
BALTIMORE, MD.



REPRINTED FROM THE  
Medical Library and Historical Journal  
VOL. 4—SEPTEMBER, 1906—No. 3

BROOKLYN - NEW YORK  
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## GERMAN-AMERICAN INFLUENCE IN MEDICINE AND SURGERY.

By JOHN C. HEMMETER, M.D., Phil.D., LL.D.,  
Baltimore, Md.



COME with me to a brief study of the history of the American people at the dawn of their existence as an independent nation. There on the battle fields of the American revolution you will find many German-American physicians and surgeons devoting their energies to the cause of freedom and aiding in the efforts of a nation's struggle from darkness and bondage to light and liberty. Those of us who frequently hear of those hated Hessian mercenaries, who were hired by England and forced to fight unwillingly against those who were struggling for independence, should not cease to emphasize that on the side for American liberty there were also large numbers of Germans who wielded their mighty swords and brought into exercise their military knowledge and experience for right against might. And as there were many German-American revolutionists, who inflicted wounds upon the British armies, there were also many German physicians and surgeons skilled to heal the wounds that the American revolutionists received in battle.

A verse of Homer says:

"A wise physician skilled our wounds to heal  
Is more than armies to the public weal."

and it was Cicero's opinion "that there is nothing in which men so approach the gods as when they give health to other men."

The well-known German epigram,

"Wo man den Arzt ehrt, kannst Du ruhig weilen  
Böse Menschen haben keine Lieder."

might be applied to the physician in this modified form:

"Wo man den Arzt ehrt, kannst Du ruhig weilen  
Böse Menschen verstehen nicht zu heilen."

The German physician and surgeon, with his classical training and endowed with the theory and practice of the most renowned universities of Germany, was much in demand by the



Americans during the Revolutionary War. To this must be added the natural inclination of medical men to be liberal minded in their political aspects—for who should understand better what are the inalienable rights of human beings than he who makes the intricate study of the body and soul his special business? After the Revolutionary War was over, and the wounds of the conflict healed, these men became even still more useful, not only in relieving suffering and combating diseases, but useful by virtue of their educational influence and the founding of institutions of learning. It is impossible within the narrow limits of this essay to give even an approximate description of the far-reaching influence of the German-American surgeons in the early part of the history of our country. An effort to do this would compel me to develop this article into a history of individuals, which is about the driest kind of history there can be; whereas my idea is that it should be a history of medical and educational principles and of results. Nevertheless it would be unfair and impracticable to omit the names of a few of these great German-American pioneers of medicine and surgery. In addition to these, there are the men, even down to the present day, who are giants of learning and medical ability, working and living in the interest of the most advanced medical progress, and in our best medical institutions. To attempt to give due credit to the genius and influence of these German-American physicians and surgeons would lead me to falter in the effort to eulogize their work, and were I to reflect on their present and future influence for good it would lead me to falter at the idea of their potency and promise.

The most elaborate panegyric would seem but a weak impertinence, reminding me too vividly of a story by Sidney Smith, who, when he saw his little grandchild affectionately patting the back of a large sea turtle, said to her: "My dear, why do you do that?" "Grandfather, I do it to please the turtle," was the answer. Sidney Smith replied: "My dear, you might as well pat the dome of St. Paul's Cathedral with a view to pleasing the dean and the chapter."

My space and time has been limited and I can only mention a few of the German medical heroes whose work has been such a blessing to our republic. Among the earliest physicians of New York State was Dr. Hosack, editor of the first medical journal in the United States. Countless valiant fighters for health, of German extraction, have been active in New York State, and

some of those who have done fundamental work are still living. Here I must mention the names of Lange, C. Herter, S. J. Meltzer, Boldt, Beck and Jacobi. In Schenectady, New York State, a monument was erected about two years ago to a German-American surgeon of prominence by the name of Von Spitzer (the Americans call him "de Spitzer"). My friend, Prof. Fred. Wilkens, then of Union College, Schenectady (now at the University of the City of New York), informs me that Von Spitzer was Surgeon-General of the colonial forces, and of the revolutionary army forces of the State of New York.

The great surgeon Wister, famed in the medical history of Philadelphia, was a German, and many most prominent in the profession in Philadelphia to-day are either German or the descendants of Germans. That magnificent surgical genius Nicholas Senn, Professor of Surgery at the new University of Chicago, and author of numerous epoch making discoveries and special works on surgery, is a German. J. Loeb, the distinguished Professor of Physiology at the University of California, research investigator of physiology and author of works of fundamental importance, was born near Bonn, on the Rhine.

The most influential German character active for the advancement of medicine in the State of Maryland during the eighteenth century was Dr. C. F. Wiesenthal, who was born in Prussia in 1726 and settled in Baltimore in 1755. It was asserted by his relatives that he had been court physician to Frederick the Great, but this is not proven. On March 2, 1776, he was commissioned by the council as Surgeon-Major of the First Maryland Battalion under General Smallwood. Certain it is that he founded the first medical school in Maryland which was located on East Fayette Street, running from Gay to Frederick Street, Baltimore. This school passed out of existence when the Medical Department of the University of Maryland was chartered in 1807. (See: *History of the University of Maryland*, by Prof. Eugene F. Cordeil.)

Wiesenthal's influence was purely local, but it was of the best. He maintained a high standard here, both by example and precept, and was the most prominent German physician in this State in the eighteenth century. He never published anything of importance; there are however, some reports of cases by him which show that he was a skilled surgeon. He was consulted by the French surgeons in difficult cases during the Revolution. His son, Andrew, was educated at St. Thomas' Hospital, London, 1786-9,

and was a noted teacher of anatomy, and also had a reputation as a surgeon. He continued his father's anatomical school in Baltimore until his early death in 1798. He was the discoverer of the "Syngamus Trachialis," a parasitic worm giving rise to Verminous Tracheo-bronchitis in fowls and birds. This was the first discovery of a parasite of an infectious disease in America. This article on the subject, dated 1797, was his only publication. Dr. Charles Frederick Wiesenthal was a zealous Lutheran and the first Lutheran church built in Baltimore owed its creation to the liberality and energy of this active physician. He was also president and physician to the German Society of Baltimore in 1784.

Dr. Conrad Small was a prominent German practitioner in Baltimore in the latter part of the eighteenth century. He was also quarantine physician. Three of the founders of the Medical and Chirurgical Faculty of Maryland were Germans—Jacob Schnively, Peter Waltz, of Washington County and John Thomas Schaaff, of Annapolis and later of Georgetown. Schaaff was the most prominent of these—born in Frederick County in 1752 of German parents, he practiced at Annapolis. He was the first Treasurer of the Medical and Chirurgical Faculty, 1799-1801, resigning at the latter date; member of Governor's Council, 1798-1800; visitor to St. John's College, Annapolis, 1802. He removed to Georgetown and was a founder of the Medical Society of the District of Columbia in 1819, and Vice-President of Columbia Institute. He practiced many years in Georgetown, and died there May 3, 1819. He was buried in the Congressional Cemetery at Washington. His tombstone refers to him as Alumnus of Edinburgh; his name does not appear among the graduates of this University, however. He was a man of great professional and social prominence. Dr. Schaaff published nothing of importance so far as I can ascertain.

Dr. Samuel Baker, of the University of Maryland, and the founder of the Medical and Chirurgical Faculty of Maryland, was the son of a German. A number of German names appear in the "Annals" among the Presidents of the Medical and Chirurgical Faculty, as, for example, those of M. S. and Jacob Baer, C. H. Ohr, W. M. Kemp, Miltenberger, Rohé, Friedenwald; and among the Vice-Presidents, Ritchie, Diffenderfer, Humrickhouse and Neuhauser. Lange and De Schweinitz are among the honorary members. There are many German names among the 2,400 embraced in the Biography of the Medical and Chirurgical



Faculty of Maryland; *e. g.*, Heldman, Hoffman, L. H. Steiner, Simon, Steinecke, Dunkel, Swope (Schwab), Uhler, Benke, Wiss, Zeller, Zollickoffer, Salzer, Reuling, Pape, Laub, Klueber, and John Morris (Moritz), Keerl (Hessian surgeon captured at Trenton—a most interesting character), Ahl (surgeon in the Revolution), Frick (Geo. and Chas.), Hitt, Hintze, Gleitsman, Erich, Ealer, Coblentz, Bruce, Boerstle, Bantz, Morawetz, Ferdinand Reinhart, Mathieu, and a host of others.

Sir Henry Sumner Maine, in speaking of the Greeks, has said: "To one small people it was given to create the principles of progress. That people was the Greek. Except the blind forces of Nature nothing moves in this world which is not Greek in origin."

This statement, like all generalizing oratoric sentiment, must be taken *cum grano salis*. There are a great many things that move in the world of our present day which are not Greek in origin. All the practical applications of steam, light, heat and electricity, which have improved the conditions of mankind so immeasurably in the nineteenth century, are by no means Greek in origin. As far as modern progress in medicine and surgery is concerned, it is almost entirely German in origin. I do not by any means desire to ignore the achievements of the Pasteur Institute at Paris, or of the Institute for Experimental Medicine in St. Petersburg, or of the meritorious research of our own country, conducted under the auspices of the Carnegie and the Rockefeller Institutes, but the work of these research laboratories constitutes but a small fraction of modern medical advancement. Even in those instances where an important new contribution has been made by a worker of another nationality, his training and education have frequently been obtained in Germany. Everyone who has lived there long enough to enter into the life of that splendid race has faith in the future of Germany, which has been, to many Americans, a second fatherland, the country of their intellectual rebirth. Particularly is this true of medical men of the United States.

As we are indebted to the German people for their character and conscience, as we are indebted to them for their probity, good faith, sincerity, earnestness, their spirit of truth, and fidelity of expression in matters scientific, so the American people owe them an enduring debt of gratitude not only for the first pioneers of medicine and surgery in this country, but for subsequent inspiration of true medical learning that has obtained uninterruptedly ever since the foundation of our great nation.

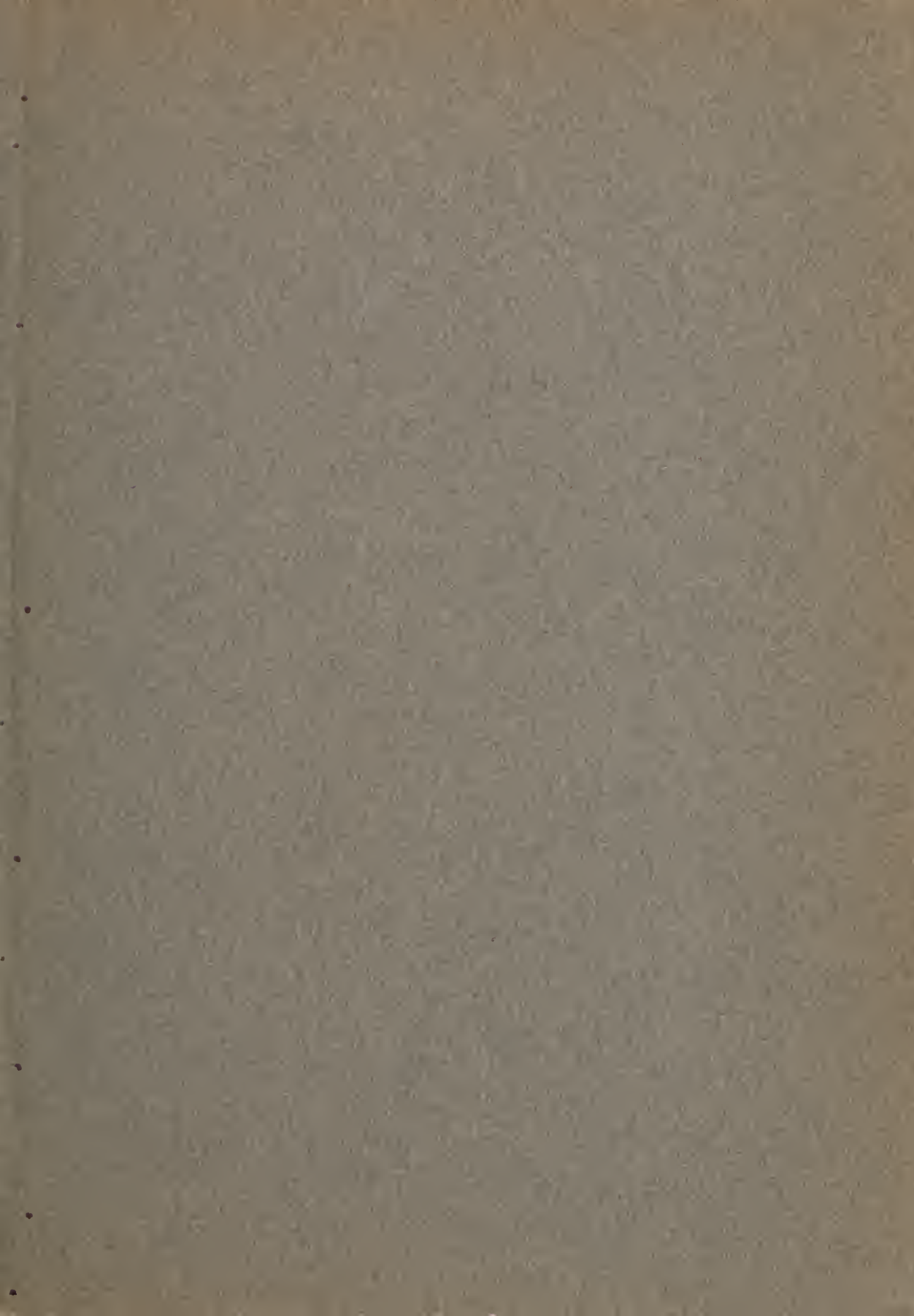


Above all things we must bear in mind that to estimate the real value of the services of the German-American physicians and surgeons we must not limit ourselves to a critical consideration of their medical and surgical work only, but it also becomes our duty to take into account their influence on general education, for in a newly organized country the first men of education and culture are generally physicians, and it is they who bring with them the beginnings of general culture.

“Heil Dir Deutscher Artz,  
Durch die Geschichte des freiesten und glorreichsten der Völker,  
Tönt dein Ruhm  
An der Wiege der Freiheit standest Du  
Durch Jahrhunderte, daure fort, dein segensreiches Wirken.”



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Nervenarzt in Berlin.

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Die

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## Neue Methoden zur Diagnose des Magengeschwürs.

Von

JOHN C. HEMMETER,

M. D. Phil. D., Professor an der Universität von Maryland, Baltimore.

Die Absicht dieser vorläufigen Mitteilung ist, eine neue Methode in der Diagnose von Magengeschwüren bekannt zu geben, welche bis jetzt noch nicht die richtige Anerkennung gefunden hat. Der hauptsächlichste neue Beitrag soll dazu dienen, die Methoden zur Erkennung des Magengeschwürs durch X-Strahlen hervorzuheben. Die drei fast beständig vorhandenen Zeichen oder Symptome des Magengeschwürs sind: Erbrechen, Gastralgia und Hyperchlorhydria, das nächst häufige Symptom ist Haematemesis. Alle diese Anzeichen können mit anderen Zuständen des Magens und sogar mit Erkrankungen von anderen Organen vorkommen, wo der Magen selbst nicht primär affiziert ist. — Nach persönlichem Studium von 400 Fällen von Magengeschwür, während einer 20jährigen praktischen Erfahrung im Hospitale und in Privat-Praxis, drängte sich mir die Überzeugung auf, dass in ungefähr der Hälfte der vorkommenden Fälle die Diagnose des Magengeschwürs mit Leichtigkeit gemacht wird; in der anderen Hälfte der Fälle ist die Diagnose schwierig und manchmal sogar unmöglich. Mit einer solchen persönlichen Erfahrung ist es natürlich, dass ich nach neuen Hilfsmitteln zu einer sicheren Diagnose, gewonnen durch Beobachtung und Experimente, suchte. Es ist meine Pflicht, zu bekennen, dass es mir passierte, dass ich Fälle verdächtiger Magenerkrankungen, welche keineswegs bestimmt als Magengeschwür erkannt und in manchen Fällen sogar als solche garnicht diagnostiziert waren, zu dem Operateur behufs explorativer Laparotomie schickte und wo trotzdem die Operation die Gegenwart von Magengeschwüren feststellte. Andererseits sind wieder Magengeschwüre vor der Operation als solche diagnostiziert worden, und es stellte sich nach der Operation heraus, dass die Anzeichen und Symptome Folgen einer ganz anderen Erkrankung waren. Während solche Irrtümer glücklicherweise selten vorkommen, deuten sie doch sehr stark auf die Notwendigkeit einer exakten Technik in der Diagnose des



Magengeschwürs. Bevor ich beginne, die Details der Differential-Diagnose zu betrachten, möchte ich bemerken, dass es mir in zwei Fällen möglich war, das Magengeschwür im lebenden Patienten zu erkennen, indem ich direkt in dem einen Falle mit dem Ösophagoskop und in dem anderen mit dem Gastroskop darauf sah. Das Magengeschwür, welches durch das Ösophagoskop gesehen wurde, war in dem Cardia-Teile des Magens, an der grösseren Kurvatur, fast direkt gegenüber dem Eingange des Ösophagus gelegen. Das andere, durch das Gastroskop betrachtet, wurde an dem pylorischen Ende des Magens, ganz nach dem Pylorus hinübergreifend, gesehen. Dieses zweite gastrische Magengeschwür wurde dort nach einer nachträglichen Operation, welche zur Milderung einer Pylorus-Stenose unternommen wurde, gefunden.

Die Technik der Untersuchung mit dem Ösophago- und Gastroskop ist schwierig zu erlangen, es gebraucht lange Übung unter einem geschickten Meister und ein sehr kostspieliges Instrumentarium. Sechs verschiedene Spezialisten in europäischen Städten haben bei den Untersuchungen den Ösophagus durchstossen und den Tod des Patienten verursacht. Eine noch grössere Anzahl von solchen Unglücksfällen können vorgekommen sein, aber diese sechs Fälle sind mir persönlich bekannt, da sie mir von den Operateuren selbst mitgeteilt worden sind. Gegenwärtig bin ich im Begriffe, die klinischen Rekorde, über 82 Fälle von Ösophagoskopie und Gastroskopie auszuarbeiten, welche von mir für verschiedene Erkrankungen des Ösophagus und des Magens gemacht worden sind. Diese Erfahrung verleitet mich zu der Meinung, dass diese Methode der direkten Inspektion des Magens sich in geschickten Händen als ein sehr wichtiger Faktor zur Entdeckung des Magengeschwürs beweisen könnte, wenn sie ungefährlich oder leichter ausführbar wäre, doch dürfte es nur bei Patienten anwendbar sein, welche noch genügend kräftig sind, die Untersuchungen auszuhalten. Bei sehr geschwächten Patienten sind diese Methoden ausser Frage.

Die Erkrankungen, mit welchen man das Magengeschwür am gewöhnlichsten verwechseln kann, sind Karzinom des Magens, nervöse Gastralgia und Gallensteine (Cholelithiasis). Die charakteristischen und zur selben Zeit meist hervortretenden Zeichen und Symptome sind: epigastrische sowohl wie dorsale Schmerzen, Erbrechen, Hemetemesis, aussergewöhnlich starke Sekretion von Salzsäure und occulte, im Darminhalt (Faeces) zu demonstrierende

Blutungen. — Ehe ich zu dem mehr technischen Teile übergehe, möchte ich hier bemerken, dass die beständige Gegenwart zweier dieser Symptome den Arzt veranlassen sollte, eine systematische Behandlung für Magengeschwür einzuleiten. Oft wird das Resultat der Behandlung beweisen, ob die Diagnose richtig war oder nicht. Die Behandlung für Magengeschwür wird keinen Schaden tun, im Falle es sich als ein Karzinom des Magens und nicht als ein Magenschwür entpuppen sollte, jedoch mit folgenden Ausnahmen: Beim Magengeschwür besteht gewöhnlich eine ausserordentlich starke Sekretion von Salzsäure, welche viele Alkalien benötigt, beim gastrischen Krebs ist in der Regel eine vollständige Abwesenheit von Salzsäure bemerkbar, welche schon viele Ärzte veranlasst hat, HCl zu verschreiben. Man kann also ersehen, dass der Gebrauch von HCl beim Magengeschwür nicht nur nichts nützen, sondern auch geradezu schädlich wirken konnte.

Ähnlichkeiten der objektiven Zeichen und subjektiven Symptome zwischen Magengeschwür und Cholelithiasis.

Die grosse Ähnlichkeit des klinischen Bildes dieser beiden Krankheiten muss jedem auffallen, der Gelegenheit hat, beide Varietäten zu sehen. Um diese Ähnlichkeit zu betonen, ist es mir möglich, auf Grund langer Erfahrung zu bemerken, dass es auch nicht ein Symptom im Magengeschwür gibt, welches nicht bei der Gallenstein-Erkrankung auch vorkommen könnte. Ich meine natürlich in solchen Fällen von Gallensteinen, welche überhaupt Symptome zeigen — und alle Symptome von Gallenstein-Erkrankungen, mit Ausnahme von Gelbsucht, können im Verlaufe des Magengeschwürs vorkommen. Dies schliesst natürlich die Tatsache ein, dass Hemetemesis und Blut im Stuhl in Fällen von Gallenstein bemerkt worden sind und dass sogar Ikterus beim Magengeschwür bemerkt worden ist, wo er in Verbindung mit grossem Blutverlust auftrat. Im Anschluss an das Gesagte ist es notwendig, zu betonen, dass Ikterus bei Gallenstein-Erkrankung ein unzuverlässiges Symptom ist. In 124 Fällen von operativer Gallenstein-Erkrankung, welche an der Universität von Maryland oder in Privatpraxis vorkamen, war Ikterus durch irgend eine Periode der Erkrankung in 60 Fällen vorhanden und abwesend in 64 Fällen. Die chemische Untersuchung des Mageninhalts gibt keine entscheidende Hülfe in der Differential-Diagnose, obwohl ein Exzess von HCl ein gewöhnliches Hauptzeichen des Magengeschwürs ist. Hyperchlorhydria wurde ge-

funden in 86 pCt. meiner Fälle, welche sich über eine klinische Erfahrung von über 312 persönlicher Analysen ausdehnt. Unglücklicherweise für die Differential-Diagnose wurde ein Exzess von HCl im Mageninhalt, auch in 74 pCt. von allen Fällen von Cholelithiasis, gefunden.

Alle die beliebten Zeichen und Symptome, subjektiv als auch objektiv, welche so lange als besonders kennzeichnend, entweder für Magengeschwür oder für Gallenstein-Erkrankung, betrachtet wurden, können uns in kritischen Fällen fehlschlagen. Es ist dieser Ursache wegen, dass ich mein Augenmerk auf neue Hilfsmittel zu einer diagnostischen Methodik richtete, um die beiden Erkrankungen klinisch zu separieren, und ich will zwei Methoden, mit welchen ich soweit genügende Erfahrung gesammelt habe, um ihre Publikation zu rechtfertigen, erwähnen. Ich setze voraus, dass sie nur in solchen Fällen notwendig sind, wo die Distinktion zwischen Magengeschwür und Gallenstein schwierig gefunden wird und wo die Möglichkeit einer anderen Erkrankung bereits ausgeschlossen ist.

Experimente, welche die Möglichkeit demonstrieren, Läsionen der gastrischen Mucosa durch X-Strahlen sichtbar zu machen.

Es ist eine bekannte Tatsache, dass Bismuthum subnitricum in Keratin-Kapseln, welches in irgend einem Teile des Verdauungstraktes vorkommt, mittels der X-Strahlen und des Fluoroskops sichtbar gemacht werden können, oder wenn nicht mit dem Auge sichtbar, doch auf photographischen Platten, die von dem Kranken aufgenommen werden, sichtbar sind. Es war nun die Frage zu entscheiden, wie dünn die Schicht von Bismuth sein konnte, um doch unter dieser Methode sichtbar zu bleiben. Durch die Gefälligkeit von Prof. Frank Martin von der Universität von Maryland, hatte ich eine Anzahl von Kaninchen und Katzen mit der vorgeschriebenen Vorsicht operieren lassen, mit der Absicht, experimentale Magengeschwüre zu erzeugen, und zwar in der Nähe des Pylorus. Im Beginne schnitt Dr. Martin einen ungefähr 1 cm breiten Ring der gastrischen Gewebe heraus und erweiterte diesen ganz um das Lumen des pylorischen Antrum, und ungefähr einen Zoll ( $2\frac{1}{2}$  cm) vom Splinkter entfernt. Das Gewebe wurde ganz bis zur zirkulären Schichte der Muscularis weggenommen und die entblösste Fläche mit einer dünnen Lage von Bismuth. subnitric. bedeckt; dann wurde die gastrische und



abdominale Wunde vernäht. Es zeigte sich, dass dieser Ring gleich nach der Operation mittels der X-Strahlen sichtbar war, später, als die Zeit fortschritt, wurde er blässer. Wenn aber das Tier nicht durch den Magen gefüttert wurde und auch kein Wasser zum Trinken bekam, konnte man den Bismuthring nach 24 Stunden und in einem Falle noch 30 Stunden nach der Operation erkennen. Das nächste Ziel war die Absicht, zu entscheiden, ob die entblösste Fläche mit Bismuth bedeckt werden konnte, indem man eine Suspension davon durch einen Gummischlauch eingoss und dem Bismuth erlaubte, sich auf die experimentale Läsion auszubreiten. Es wurde konstatiert, dass dies möglich war, vorausgesetzt, dass das Bismuth nicht später als 48 Stunden nach der Operation eingegossen wurde. Bei Hunden, Katzen und Kaninchen breitet sich zu dieser Zeit eine hervortretende Granulation aus, welche fast die ganze Basis des experimentalen Magengeschwürs ausfüllt. Bei einigen Hunden, welche zu einer zweiten Operation gebraucht wurden, zeigte es sich, dass zwei Wochen nach der Erzeugung des experimentalen Magengeschwürs die Läsion vollständig verheilt war. Kaninchen sind für solche Versuche nicht praktisch, da sie die Operation nicht gut vertragen können.

Durch diese Experimente wurde es klar, dass ein Substanzverlust der gastrischen Mucosa, welcher sich bis zur Muscularis mucosae ausdehnt, durch die Bismuth-Methode sichtbar gemacht werden konnte, und dass das Bismuth in genügender Quantität an der Basis des experimentalen Magengeschwürs klebte, um die X-Strahlen für 24 Stunden auszuschliessen, vorausgesetzt, dass keine Nahrung gegeben wurde.

Wenn wir in Betracht ziehen, dass beim Menschen das gastrische Magengeschwür nicht nur einen Substanzverlust, welcher sich abwärts bis zur muskulösen Schicht erstreckt, bedeutet, sondern dass die Ränder der Magengeschwüre auch erhaben sein können über die gewöhnliche Fläche der Schleimhäute des Magens, durch entzündliche Induration, so dass der Ulcus einen Krater bildet, werden wir die Möglichkeit erkennen, diese Läsion mit X-Strahlen und dem Fluoroskop sichtbar zu machen, nachdem das Magengeschwür mit Bismuth. subnitric. gefüllt worden ist.

Dabei muss noch angeführt werden, dass beim Menschen auf den Granulationen auf der Oberfläche der Magengeschwüre sich gewöhnlich ein agglutinierendes Transsudat ausscheidet, welches die Bismutpartikel mechanisch festhält.



Demonstration des Magengeschwürs beim Menschen mittelst der Bismuthsubnitrie und X-Strahlenmethode.

Drei Fälle von zweifellos gastrischem Magengeschwür wurden zu dieser Arbeit benutzt. Der Patient bekam ein grosses Glas voll warmen Wassers zu trinken, in welches ein gehäufter Teelöffel von Bismuth. subnitricum gerührt wurde. Dies muss geschehen, ehe irgendwelche Nahrung genommen ist, am besten vor dem Frühstück. Nach dem Schlucken dieser Bismuthsuspension muss sich der Patient für eine halbe Stunde niederlegen, erst auf den Rücken, und wenn die nachträgliche Fluoroskopie kein dunkles Feld ergab, wurde dem Patienten bei der nächsten Untersuchung gesagt, auf dem Bauche zu liegen, und sollten noch weitere Untersuchungen notwendig sein, ist die linke und rechte laterale Stellung geraten. Wenn an einem Tage eine Bismuthuntersuchung gemacht worden ist, ist es nicht anzuraten, sie am nächsten Tage zu wiederholen, weil, obwohl die Methode dem Patienten nichts schadet, das Bismuth bis zum nächsten Tage schon das Colon erreicht haben kann, und indem man es dort sieht, könnte es eine diagnostische Täuschung veranlassen. Eine gewöhnliche Erfahrung, nachdem man ein Glas voll von der Bismuthsuspension auf diese Weise gegeben hat, ist folgende: Der ganze Magen kann in vollständiger Weise sichtbar werden. Dies kommt besonders bei kleinen Mägen vor, nachdem der Patient auf einem Sofa gerollt worden ist, um das Bismuth über den ganzen Magen zu verteilen. Wenn ein Magengeschwür gegenwärtig ist, kann der erfahrene Fluoroskopist ein kleineres Feld von etwas dunklerer Farbe im allgemeinen dunklen Teile, welches mit dem Magen korrespondiert, entdecken. Das Bismuth, welches den gesunden Teil des Magens bedeckt, verschwindet in drei bis sechs Stunden, vorausgesetzt, dass keine Nahrung gegeben worden ist, aber in dem Felde, welches mit dem Magengeschwür korrespondiert, kann das Bismuth mit den X-Strahlen noch 24—36 Stunden später erkannt werden, da die gastrische Peristalsis es nur sehr schwierig entfernen kann.

Einer dieser Fälle, in welchem in dieser Weise ein Magengeschwür diagnostiziert wurde, war bei einer jungen Dame, welche später für mich von Dr. John B. Deaver in Philadelphia operiert und wo ein grosses Magengeschwür im Zentrum des Pylorus gefunden wurde. Damit das Bismuth sich in der durch das Magengeschwür verursachten Depression deponieren kann, sind zwei Dinge notwendig: Die Suspension von Bismuth soll kon-

zentriert und der Patient lange Zeit in einer Position verbleiben; da annähernd 78 pCt. aller gastrischen Geschwüre entweder an der kleineren Kurvatur, hinteren Wand des Magens, oder im Pylorus vorkommen, ist es angezeigt, den Patienten zuerst in der Rückenlage mit etwas erhöhtem Becken, und dann auf die rechte Seite zu plazieren, was veranlasst, dass sich ein Niederschlag von Bismuth an den benannten Stellen absammelt. Ein weiterer Faktor von grosser Wichtigkeit ist die Geschicklichkeit und Erfahrung des Fluoroskopisten. Man soll nicht erwarten, klar begrenzte und auffallende dunkle Felder zu sehen. Die Schatten, verursacht bei einigen experimentalen Läsionen in dem Magen, waren nicht so dunkel, als jene, welche von den Rippen oder der Wirbelsäule erzeugt wurden. Es folgt daraus, dass, wenn ein Magengeschwür unterhalb einer Rippe zu liegen kommt, es schwierig sein wird, dasselbe zu beobachten.

Nach dieser Methode bildet die Leber kein Hindernis zur Entdeckung der Geschwüre, weil ein Magen mit experimentalem Magengeschwür, die so plaziert sind, dass sie ganz von der Leber des Tieres verdeckt werden, bewundernswerte Objekte für die Praxis des Entdeckens der künstlichen Magengeschwüre bildet. Da die Methode nicht nur unschädlich, sondern dem Patienten auch gut tun kann, fühle ich mich berechtigt, sie als Mittel zur Diagnose zu empfehlen. In Fällen, wo die klinische Geschichte, chemische und physikalische Zeichen auf ein Carcinoma des Magens deuten, können die Ulcerationen, verursacht durch das Karzinom, falls solche vorhanden sind, auf dieselbe Manier sichtbar gemacht werden. Die Differentialdiagnose zwischen Magengeschwür und Krebs verlangt die Berücksichtigung aller chemisch-mikroskopischen Beweise über den Mageninhalt, welche man nur erlangen kann. Es wird nicht viele Jahre nehmen, und wir werden eine Methode zur Diagnose des Krebses mittelst einiger biochemischer Zustände des Blutplasma oder Blutkörperchen besitzen. Wo das Fluoroskop zuweilen versagte — dem Auge die Anwesenheit und Lage des Geschwürs zu enthüllen — gelang es in zwei Fällen noch — durch photographische Aufnahme des mit Bismuth ausgeschwemmten Magens — das Ulcus zu entdecken. Zum Schluss möchte ich noch bemerken, dass es nicht gelang, Gallensteine fluoroskopisch zu erkennen, und zwar versagte diese Methode in zwei Fällen von Cholelithiasis, bei welchen man später die Gallensteine operativ entfernte.

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Die  
**physiologischen und pathologischen Beziehungen**  
der  
**weiblichen Sexualorgane**  
zum  
**Tractus intestinalis**  
und besonders zum Magen.

Von

**Dr. ERWIN KEHRER**

Privatdozent an der Universität Heidelberg.

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**Deutsche med. Wochenschrift:** In dieser sehr umfangreichen und überaus fleissigen Arbeit gibt uns Verfasser die Resultate seiner Untersuchungen über die physiologischen Beziehungen (I. Teil) und pathologischen Beziehungen (II. Teil) zwischen den weiblichen Genitalien und dem Magen-Darmkanal. Etwa 650 Einzeluntersuchungen des Magens in Bezug auf seine Veränderungen, Sekretion, Motilität, Pepsinabscheidung etc., während der Menstruation, Schwangerschaft und Wochenbett, bei Vomitus, Ptyalismus, Hyperemesis gravidarum, bei Hämatemesis, unstillbaren Diarrhoen, Blutdurchfällen in der Schwangerschaft und bei gynäkologischen Erkrankungen wurden mit der Kussmaulschen Magenpumpe nach Probefrühstücken oder nach Probemahlzeiten ohne jeglichen schädlichen Einfluss auf die Fortdauer der Schwangerschaft vorgenommen.

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Oberarzt an der I. medizin. Universitätsklinik in Berlin.

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# AUTO-INTOXICATION FROM THE GASTRO- INTESTINAL TRACT

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HISTORICAL VIEWS CONCERNING THIS SUBJECT—TRUTH  
AND ERROR CONCERNING THE THEORIES  
OF AUTO-INTOXICATIONS

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JOHN C. HEMMETER, M. D., PH. D., LL. D.  
Baltimore, Md.

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Reprint from the OHIO STATE MEDICAL JOURNAL, July, 1906

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The Berlin Printing Co., Columbus, Ohio



## AUTO-INTOXICATION FROM THE GASTRO-INTESTINAL TRACT.\*

### HISTORICAL VIEWS CONCERNING THIS SUBJECT — TRUTH AND ERROR CONCERNING THE THEORIES OF AUTO-INTOXICATIONS.

BY JOHN C. HEMMETER, M. D., PH. D., LL. D.  
Professor of Physiology and Clinical Medicine,  
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[Address on Medicine before the sixty-first annual meeting of the Ohio State Medical Association, May 9 to 11, 1906, Canton, Ohio.]

#### PRE-GALENIC MEDICINE.

Our conceptions and the doctrines which we have formulated concerning the nature of diseases, have undergone manifold changes during the past century. Before the era of bacteriology the doctrine which seemed to have the firmest hold upon medical thinking was the ancient theory of the Dyscrasias. We see traces of this hypothesis in the writings of Hippocrates. The real significance of the term was a depraved or abnormal state of the blood. The entire pre-Galenic medicine might be said to be comprised in the achievements of Hippocrates, Diokles, Herophilos, Erasistratos.

#### THEORY OF POISONOUS HUMORS.

One of the principal achievements of Galen was the construction of the thinking of those four great classical physicians into a system, and this system culminated into the doctrine of the Dyscrasias. Among the

last of the more modern representatives of this ancient doctrine was Rokitansky. The principal idea underlying the whole conception was that the juices of the body, particularly the blood, could undergo such changes that it contained poisonous humors; we could call them toxic substances, to the agencies of which the various diseases were due.

#### ERA OF BACTERIOLOGY.

About fifty years ago, Virchow's genius gave the deathblow to this so-called humoral pathology. Then gradually developed the era of bacteriology, in which the morphologic study of the bacteria and other living disease producers occupied the interests of medical workers. Recently bacteriology has arrived at a critical parting of ways, one of these leads to the doctrine of the disease toxins or chemical poisons derived from the cells of the organism itself, substances which the living body produces during its own life processes—and these are the auto-intoxications proper.

#### TRUE AUTO-INTOXICATIONS.

When toxic substances are produced in the internal laboratories of the body, but by living organisms introduced from the outside, these cannot strictly be classed among the auto-toxic substances. Thus diphtheria and tetanus and their toxins cannot logically be classed among the auto-intoxications; for it is not the cells of the organism which produce the poison in this case; but uræmia, eclampsia, gout and diabetic coma are true auto-intoxications.

\* In the preparation of this address I have drawn largely from articles published by me in my Text-books on DISEASES OF THE STOMACH and INTESTINES in the "INTERNATIONAL CLINICS," Vol. II, 12th Series, in the ARCHIV f. "VERDAUUNGS-KRANKHEITEN," and other German and American journals.



NATURE AND CONCEPT. The history of medicine is extensively a history of studies and inquiries into the origin of disease. The processes which have been recognized as inducing disease have been relegated to four types. These pathogenic processes are named in the order of their importance: (1) Infections; (2) disturbances in nerve reaction; (3) disturbances in nutrition; (4) primary elementary dystrophies. More and more the agency of infection has encroached upon the domain of the other three pathogenic factors. At the present day the truths that are known or believed to be known concerning infection, do not suffice to explain the origin of disease; not only of disease in general, but we are unable in each and every case to explain the origin even of such diseases which we have many good reasons to believe are infectious in origin.

At the beginning of the nineteenth century the ancient views of humoral pathology and the doctrines of dyscrasias still occupied the medical mind. The endogenous causes of disease were thought to be abnormal compositions of the blood, secretions and tissue juices. As this view was gradually replaced by investigations based upon the natural sciences, pathology acquired a more exact and precise foundation. The evolution of cellular pathology brought with it the development of the chemistry of the cell, that is, of the chemical physiology and pathology. Even later, when bacteriology, the most recent daughter of cellular pathology, arose and seemed to absorb the doctrines of its mother science; cellular chemistry asserted its rights. In the search for the origin of the disease by the aid of modern cellular pathology and bacteriology, the chemical nature of the "materies morbi" could not be pushed to the background.

It required several decades before the technique and rough foundations of bacteri-

ology were happily surmounted. But even during this time Pasteur repeatedly emphasized that the material which is essential to the existence of even an infectious disease is of a chemical nature.

Organic cell life is comparable to a chemical factory. From introduced raw materials it manufactures those substances which are required for the maintenance of the organism. These are incorporated in the tissue juices and protoplasm. During the process of cell life and the performance of all functions, waste products are formed; these are excreted and removed from the cell body and eventually from the organism. Intake and output, assimilation and growth, destruction and breakdown of protoplasm by function—anabolism and catabolism—these terms comprise the life history of the cell. But all these processes, although inseparably connected with the morphological elements of the cell, are in their innermost nature nevertheless chemical processes. Even the life and activity of the bacteria must be considered in the light of chemical processes. The bacteria, *per se*, may cause an infection; they may produce primary metastatic foci of disease also, but these disease foci are as a rule local, for the general disseminated phenomena of these diseases are always caused by toxic metabolic products of the bacteria. These may originate within the body of the bacteria themselves, or they may be produced from the constituents of the animal cells in and upon which the bacteria are parasitic.

In modern medical literature we find a superabundance of publications directed toward the recognition of external causes of disease. When one sifts the result gained thereby, one cannot fail to be impressed with the fact that they, by no means, suffice to explain the origin of many diseases. After all, the facts of etiology, derived from a study of infection, disturbances in nerve reaction, disturbances in

nutrition and of primary elementary dystrophies have been brought together, a large number of diseases remain for which no satisfactory explanation as to their origin has been offered. The so-called external causes of disease are particularly insufficient to explain those pathogenic disturbances which arise from some internal detriment or abnormal change. At this point we begin to seek the cause of the disease within the cell itself.

#### DEFINITION OF AUTO-INTOXICATION.

Auto-intoxications, in the strict sense, are morbid conditions which originate by the agency of toxic products of metabolism in the organism itself, and in the etiology of which the direct activity of micro-organisms can be excluded. Among the safe examples of such auto-intoxication we can classify only such endogenous diseases of which the etiologic poison or toxine is known. A knowledge of these toxines is the *sine qua non* for the existence of an auto-intoxication. Strictly speaking, therefore, there are only three conditions which can logically be considered auto-intoxications. These are (1) *ammonemia*, the supersaturation of the blood with carbonate of ammonia, which is formed from urea, according to Treitz, within the intestinal canal and is absorbed into the circulation; (2) *hydrothionemia*, which is the absorption of sulphuretted hydrogen ( $H_2S$ ) from the intestine, and (3) *diabetic coma*, which is most probably produced by the formation of beta-oxy-butyric acid, in the course of diabetes mellitus. With a little stretch of the imagination, three abnormalities of metabolism may be included which do not run their course with intoxication symptoms of the general organism. These are *cystinuria*, *alcaptonuria* and *oxaluria*. In my opinion these conditions cannot be considered as independent diseases peculiar to themselves. Not one of them can, in the

present light of our knowledge, be considered a disease *sui generis*. Von Jaksch ("Die Vergiftungen," in Nothnagel's Spec. Path. u. Ther., Bd 1) would include under the auto-intoxications also acetone-mia and uricacidemia (1 c., p. 624). Under the heading of uricacidemia he makes the statement that there are diseases in which the most prominent phenomenon is the occurrence of increased quantities of uric acid in the blood, as well as in the urine. This statement, that uric acid occurs in the blood, is no doubt a lapsus linguae, for in none of the literature quoted by von Jaksch, nor in other literature known to me, is a satisfactory evidence given that uric acid, as such, occurs in the blood. This lack of preciseness of von Jaksch has no doubt been partially the cause of the widespread error that uric acid occurs in the blood as such. What this celebrated clinical chemist evidently intended to say was that uric acid occurs in the blood in certain diseases in the form of sodium bi-urate or quadri-urate.

#### SIGNIFICANCE OF THE DOCTRINES OF GASTRO-INTESTINAL AUTO-INTOXICATION.

In order to establish the existence of an intestinal auto-intoxication, we have a right to demand two clinical proofs: (1) The demonstration of the poison or toxine itself; (2) the demonstration that the locality of its formation is in the gastro-intestinal tract. Unfortunately these two requisites have not been supplied in a great many of the diseases which Bouchard, the originator of the doctrine of auto-intoxication, classes among these abnormalities. The evidence furnished by Bouchard and others in support of their doctrine may be separated into experimental and clinical evidences.

#### CRITICISM OF THE EXPERIMENTAL EVIDENCES.

—I have already stated that the doctrine of auto-intoxication, in order to

acquire a safe foundation that would entitle it to the claim of being an intrinsic part of didactic medicine, would be the demonstration of the poison, and secondly the demonstration of its source. Not until these two requisites are fulfilled can the claim of the theories of auto-intoxication to clinical citizenship, as it were, be conceded. Hitherto the advocates of this hypothesis have thought that the evidence was sufficient if they found a poison in the urine. Very many times they did not isolate this poison, but contented themselves with efforts to prove that the urine was toxic for certain lower animals. What is necessary, however, to make the theory acceptable to conservative clinicians, is not the demonstration of a toxic property of the urine, but of an isolated toxine from the urine, and the demonstration of the same toxine at the place of origin of the disease. Frequently the toxine is not at all demonstrable at the original location of the disease. For instance, if it has developed in the stomach or intestine it may have been expelled by vomiting or purging. Recently, however, W. B. Halliburton and John F. McKendrick (*Brit. Med. Journal*, June 29, 1901) have isolated from the gastric contents of a patient suffering from benign pyloric obstruction and tetany, a toxic substance that, when injected into an animal, produced a marked fall of blood pressure and slowing of the heart-beat. This substance was not present in the normal gastric contents at health, and after neutralization of a solution of this toxine, no fall of blood pressure was obtained on animals. The attacks of tetany in this patient ceased after an operation was performed on the stomach, which restored the downward progress of the ingesta. The pyloric obstruction had developed as the result of a cicatrix of an old gastric ulcer. Dr. W. B. Halliburton, whom I had the pleasure of

meeting in London in 1900, is a physiological chemist whose work has been characterized by admirable preciseness and conservatism. I am disposed to attribute much importance to his results furnishing the first evidence that gastric tetany really is the result of auto-intoxication. This case is an instance of the discovery of the poison at the source of origin of the disease and not in the urine. Albert Albu makes the statement that the positive finding of toxicity of the urine includes a local origin (meaning as a rule the gastro-intestinal tract) of the poison and its resorption (*Ueber die Auto-Intoxication des Intestinal Tractus*, p. 197). In opposition to this statement I must emphasize that the presence of a toxine in the urine does not necessarily include a local origin of the poison and its resorption, for there are undoubted toxins which arise in the circulating blood itself, or in such a disseminated manner throughout the body, that they are born, as it were, directly into the circulation, and do not require absorption; for we can only speak of absorption where a substance is drawn into the blood or lymph circulation either from the gastro-intestinal tract, or from one of the hollow organs of the body or from cavities that have been formed under pathologic conditions. We certainly are not justified in speaking of a local origin of the poison in such conditions as uric acid poisoning, chlorosis, cystinuria, etc., conditions which Albu classes among the auto-intoxications and the origin of the toxins of which is not even known. For although Brieger and Stadthagen assert cystinuria to be an intestinal mycosis, they furnish no satisfactory evidence. It is unsafe to speak of local absorption of a toxine in any disease the direct cause of which is unknown.

Another weak point in the auto-intoxication theory is that only in the three con-



ditions mentioned, viz, ammonemia, hydrothionemia and diabetic coma, have the symptoms been traced to anything like a specific poison. The advocates of the theory explain this by the well known fact that a toxic substance, after having been absorbed from its original source, may undergo manifold transformations before it is excreted in the urine, so that widely different substances appear in the urine from those which were originally formed in the body. For instance, in acute yellow atrophy of the liver, leucin and tyrosin appear in the urine. These are products of albumin breakdown. But it is certain that these substances do not cause the disease symptoms, for when leucin and tyrosin are injected into the blood vessels of animals, no detrimental effects on the nervous system have been noticed (Frerichs, Panum, Billroth). These substances are simply the expression of an extensively altered metabolism. In fact, in acute liver atrophy the experiment of functional exclusion of the liver has been carried out by the disease in the human being. All the substances that are brought to the liver from the digestive canal are no longer transformed by this organ. They are permitted to reach the blood current in the unassimilated form of the intermediate substances of metabolism. These intermediate substances appear in the urine in place of the end product of the oxidation of the albuminous bodies. During acute yellow atrophy the urea in the urine becomes less and less, and occasionally disappears entirely, and these intermediate substances take the place of urea. I mention all this to show that what is found in the urine cannot always be attributed to the original source of the disease. As further examples of the transformation which absorbed substances undergo during their passage through the circulation to the urine, the following may be cited: Beta-oxy-buty-

ric acid may be excreted as diacetic acid and acetone, salol will be excreted as salicylic acid and phenol, benzoic acid will be excreted as hippuric acid, etc.

The toxic products of the decomposition of carbohydrates in the stomach and intestines are so small in quantity and are, in addition to this, so largely diluted in the blood, that it requires a considerable effort of the imagination to conceive of a detrimental effect of these products upon the general organism. One of the most frequent products of carbohydrate fermentation, lactic acid, is never found in the urine, not even in cases of gastric carcinoma, in which it is formed in considerable quantities in the stomach. It can accordingly not be assumed that it is absorbed in considerable quantities; or if it is, we must assume that it undergoes some transformation. At least I may say that I have never found lactic acid in the urine when this acid was present in the stomach contents by the Uffelmann test. No convincing proof is furnished for the theory of intestinal auto-intoxication by experiments attempting to demonstrate the effect of alcoholic extract or urine and feces upon animals. In a great many of the experiments recorded it is not difficult to recognize that these extracts have been made poisonous by the materials employed in their preparation, Normal urine and normal feces, when injected in sufficient quantities, are of necessity poisonous for small animals; conservative men will fail to see any proof, in such experiments that the individual from whom these excretions were taken suffered from auto-intoxication. The experiments which tend to show that indol (indican) and skatol are poisonous for the organism, are totally fallacious, for it takes one gram of these substances per kilo weight of rabbit to produce intoxication symptoms. In a human of medium weight sixty grams of



indol would be necessary to produce toxic phenomena. As a matter of fact, the total quantity produced in the intestine only amounts to a fraction of one gram. A curious deficiency is observable in all of the reported cases of hydrothionemia, which is put down by Albu (l. c., p. 125) as an intestinal auto-intoxication, of which the exact proof has been furnished by Friedrich Betz ("Memorabilia," 1864, p. 140). This is the condition upon which Senator founded his conceptions of self-poisoning of the organism (Berliner klin. Wochschr., 1884, No. 24). In all the cases of hydrothionemia that I could find recorded in literature the  $H_2S$ , or hydrogen sulphide was discovered in the urine and noticeable by the odor of the eructations and in the expired air. Right here we might call attention to the fact that if a patient eructates sulphuretted hydrogen, his breath will very frequently contain this gas, but this cannot, in my opinion, be considered an evidence that the gas has been absorbed into his circulation and is expired by his lungs. Most observers gravely mention that the  $H_2S$  is also contained in the feces, but not one test of the blood for  $H_2S$  is on record. With proper chemical methods, very little  $H_2S$  could be detected, if it were contained in the blood. The assumption that the hydrogen sulphide is contained in the blood is based upon the demonstration of this substance in the urine. It is argued that it could not appear in the urine unless it had reached the kidney by way of the circulation. My personal experience with the study of the intestinal gases is that even under pathologic conditions  $H_2S$  is not produced in large quantities in the intestines. (See Hemmeter, "Diseases of the Intestines," Vol. 1.) Some years ago Bergeon conceived the idea of treating with  $H_2S$  the pulmonary tuberculosis patients at Bay View Hospital, Baltimore, while I was

physician in charge of that institution. The  $H_2S$  did not heal this pulmonary phthisis, nor did it exert any toxic effect upon the individuals into whom it was injected, but its effect on the attending physician and nurses was disastrous; so much so that this disagreeable feature, more than anything else, soon caused the cessation of the experiments.

How far the enthusiasts on the theory of intoxication may drift from sound logic is shown in the experiments of Charrin, who observed severe symptoms after injections of distilled water into the veins, in the report of which he explains, "Even water is a poison," and he adds a detailed list of our articles of diet, showing how much of this "poison" is contained in each one of them.

**AUTO-INFECTION VERSUS AUTO-INTOXICATION.**—In many cases where the clinician is confronted with a group of symptoms, the etiology of which is not at once clear, it is difficult to decide whether he is dealing with an auto-infection or an auto-intoxication. It may be claimed that a febrile course, longer period of incubation, swelling of the spleen, relapses, etc., speak for infection. The toxalbumins and the albumoses when they are absorbed from the intestinal tract, it is true, do not produce such effects, as a rule. But there are poisons known which require a period of incubation of several days before the development of their characteristic symptoms. Then again, there are even pure intoxications which may run their course with fever. We are then restricted to the demonstration of inflammation or of bacteria in the blood, as the only real evidence of an existence of an auto-infection. The intestinal canal, stomach and even mouth contain, at all times, very large numbers of micro-organisms. (See article, "Intestinal Bacteria," in Diseases of the Intestines, Vol. 1, by Hemmeter.)

Drs. Harvey Cushing and Louis E. Livingood have asserted that an a-microbic state can be brought about in the gastrointestinal canal by dietary precaution, sterilization of the food, etc., disinfection of the mouth, lavage of the stomach, taking of sterile food from sterile dishes, etc. The details of their methods are given in "Contributions to the Science of Medicine," dedicated to William H. Welch, p. 574. These observers base their conclusions upon the negative results of cultures either from the contents of the intestine or from the surface of the mucosa. That the gastric and duodenal flora and fauna may be considerably diminished by dietary precautions, disinfection of the mouth and gastric lavage, there can be no doubt but that the exemption from peritonitis, after any abdominal operation, is directly attributable to this partial asepsis, is questionable; for in all cases the operators (Halsted and Finney) took every precaution of surgical asepsis to avoid infection. These experiments were conducted with admirable regard for bacteriological technic, and have shown the importance of an amicrobic diet and gastric lavage as preparatory treatment to operations upon the gastro-intestinal tract. They have not satisfactorily demonstrated that the digestive canal may be so far rendered amicrobic as to render the precaution of surgical asepsis less peremptory. Cultures taken from the surface of the stomach and the surface of the duodenum may be negative, and yet there may be bacteria in the depths of the mucosa. This much has been conclusively proven after sterilization of the human hand the deeper layers of the skin will always contain bacteria even after antiseptic scrubbing, etc. I have been able to demonstrate as much in experiments upon the colon of dogs. After lavage of the colon with antiseptic solutions from an artificial or experimental anus to the true or

normal anus, and total exclusion of ingesta from the colon for three weeks, cultures taken from the mucosa of the ascending and descending colon were positive. (See J. C. Hemmeter "Etudes Experimentales," etc., etc., *Bacteries Proteolytiques du Colon*," XIII Congress International de Medicine, Paris, 1900, section de Pathologic Interne," page 133 to 149.) The difference between the results of Cushing and Livingood and myself may partially be explained by the different portions of the gastrointestinal canal upon which we worked. The duodenum and jejunum are naturally freer of bacteria than the colon, and surface areas may be found in the duodenum which are perfectly sterile to cultures, even in the absence of any preparatory amicrobic dieting and lavage. Just what brings about this localized surface asepsis in the intestines under normal conditions is not known, but it seems probable that there is a normal disinfecting power to the intestinal canal, attributable, perhaps, to substances in the digestive secretions that have an antitoxic action. The natural defense against bacteria may be injured by medicinal antiseptics, purging, etc. (See R. Schultz, *Berliner klin. Wochenschr.*, 1900, No. 25.)

The bacteria of the digestive tract may cause grave disease phenomena when they enter the system. Desobry, Nocard and Porcher have asserted that battalions of micro-organisms penetrate into the lymphatic vessels and blood during the absorption of the food products, but that they are made harmless in the lungs and other organs or excreted with the urine. If the vitality of the tissue is reduced, these bacteria may cause disease. Bouchard and Charrin explain the great majority of all those diseases which are not caused by specific infectious excitants, like gonorrhea and tuberculosis, by such auto-infection with the bacteria of the mouth and gastro-intestinal tract. Accordingly we may include

among the auto-infections pneumonia, meningitis, bronchitis, pleurisy, furunculosis, otitis; even diphtheria has been classed among the auto-infections on the ground that the mouth always contains diphtheria bacilli. What paradox conclusions such wild hypotheses may lead to, may be judged from the expression of Charrin (see *Verhandlungen des XVI Congresses f. innere Medicin, Wiesbaden, 1898, p. 158*), viz: "Healthy man is enabled to defend himself against the numerous infectious excitants which he continually carries in his organs. *He first becomes sick when he is no longer well.*"

In the second volume of my work on Diseases of the Intestines I have stated the conditions under which the intestine becomes permeable for bacteria. I might repeat here that under normal conditions the chyme, the chyle and the blood, as well as all the organs, remain free of micro-organisms, even after food has been taken which is very abundant in bacteria. There are very virulent bacteria which can penetrate the intestinal walls and enter the blood. This is proven by the occurrence of intestinal anthrax in animals and of enteric fever and intestinal tuberculosis in man. In the course of intestinal occlusions and hernias, as well as of gastro-enteritis in children, the blood may contain bacteria which have originated in the intestines. It is conceivable that reduced vitality of the tissues may pave the way for intestinal auto-infection, thus extreme exhaustion, debility from old age, abrupt reduction of temperature, may facilitate the invasion. Pritsch has made the statement in this connection, which is almost as paradoxical at first sight as that of Charrin just quoted, viz: "That laparotomy patients did not die because they became septic, but they became septic because they died." The conclusion that a diphtheria or an erysipelas, in any particular case, is an auto-infection, because streptococci or diphtheria bacilli are found in the

mouth of normal individuals, is not absolutely correct. It fails to take into consideration the distinction between pathogenic and non-pathogenic micro-organisms of the same species. A large number of the micro-organisms of the mouth and intestine do not grow on common culture mediums. The most recent investigations of Escherich have shown that it is not probable that the harmless form of the colon bacillus may become virulent, but that in all cases of grave enteritis or cholera nostras, there was a greater probability or even sureness that these virulent bacteria were introduced in the food from the exterior, and did not develop from the harmless form. The organism has become immuned to the products of such bacteria as are normal inhabitants of its intestinal canal. Much more importance must be attributed to the introduction of bacteria and their products from the outside, in the etiology of infections, than from those saprophytes which are normally present in the intestines. We may distinguish these various infectious agents the *imported* and the *domestic* micro-organisms, the latter being those which are normally present in the intestinal canal. In my opinion the products of the domestic saprophytes rarely become dangerous for the organism.

CRITICISM OF THE CLINICAL ARGUMENTS IN FAVOR OF AUTO-INTOXICATION. —The recognition of intestinal auto-intoxication has been based upon the (1) manifestation of gastro-intestinal disturbances, and, (2) attempts at demonstration of toxic products in the urine and blood, as well as (3) efforts to demonstrate that the extract made from feces, urine and gastric juice were toxic when injected into experimental animals. Conservative critical judgment of three main supports for the diagnosis of intestinal auto-intoxication shows that they are extremely variable factors. In the first place, if a disease has begun with vomiting and diarrhea, this is by no means signifi-



cant of an auto-intoxication, for these gastro-intestinal disturbances may occur secondarily in all infectious diseases. The presence of an excessive amount of ethereal sulphates and indican has been taken as an indication of auto-intoxication, but v. Pfungen, Albu and myself have shown the fallacy of this criterion. The amount of ethereal sulphates and indican depends upon the frequency and volume of the evacuations, and it is one of the most variable factors in clinical pathology. It is true the ethereal sulphates are the product of albumin putrefaction in the intestine, but the combination of the products of albumin break down with sulphuric acid show very little toxic property; they may be present in large quantities in the urine without any auto-intoxication symptoms. The speculations which attribute migrain, epilepsy, skin diseases, chlorosis, to intestinal auto-intoxication, because the conjugate ethereal sulphates are abnormally increased in the urine, are devoid of objective proof. Many of the symptoms hitherto attributed to auto-intoxication from the intestine, are identical with those which were formerly classed as due to a "reflex." An interesting polemic has sprung up at the fourteenth Congress for Internal Medicine, Wiesbaden, 1898, as to which symptoms could be considered as due to reflex and which to intestinal auto-intoxication. Much of this polemic consists of hair-splitting discussions without practical end. Some symptoms, however, follow so promptly upon well known causes other than auto-intoxication, that we must of necessity classify them as reflexes. For instance, when Beaumont touched the wall of the stomach of the wounded hunter, Alexis St. Martin, with a thermometer, he could produce vertigo, pallor of the face, fainting and obscurity of vision. No change was observable in the stomach itself, while these systemic effects were produced. This can hardly be termed anything but a reflex. Such phenomena

occur rapidly, and as a rule following promptly upon the irritation that provokes them. But then if we wish to assign similar phenomena to intestinal auto-intoxication, we will have difficulty in explaining the promptness of their occurrence when we consider the slowness with which such toxins pass the intestinal wall and liver.

HEALING THE PROTECTIVE FUNCTION OF THE LIVER.—The liver offers a strong barrier to the entrance of toxic substances. In order to understand what the organism suffers when the functions of the liver are lost or eliminated, we will have to know all those useful and beautiful things which the liver accomplishes when in a state of perfect health. Unfortunately those functions are imperfectly understood. But judging even from those few well-ascertained facts that we are fortunately in possession of, we can readily conceive that the liver is an organ secondary in importance only to the heart, for human life. Living things can do without stomachs; they can live for forty days without eating at all, but mammalia can only live a few days, sometimes not twenty-four hours, without a liver.

I shall not speak of its bile-forming and bile-excreting functions, of its glycogen formation, nor the hepatic generation of urea, three functions of far-reaching importance. I shall not even speak of the digestive, nutritive and assimilative functions of the liver. A very large part of the albuminous products of gastric and intestinal digestion undergo a secondary digestion and transformation in the liver. We may conceive this organ as passing judgment upon these products, whether they shall be considered fit or not to enter the general circulation, for absorption by the cells of the various tissues. The portal circulation brings a large variety of digestive products from the intestinal canal which undergo further chemic changes in the hepatic parenchyma. If the gastric and intestinal digestion is so abnormal that the results of this digestion



in the alimentary tract furnishes incomplete bodies, substances immature and far from being congenial to the cells of the tissues, the liver, in its efforts to reform them, may become overworked. In certain intensely infectious diseases, like dysentery or typhoid fever, the products of bacterial decomposition will be added to those of a defective digestion, and a condition of absolute loss of function of the liver may supervene. I have spoken of this as "paralysis of the liver."

THE "DYSPEPTIC LIVER."—A few years ago, Bouchard and Hanot called attention to a peculiar enlargement and induration of the liver which occurred in the course of chronic gastric and intestinal dyspepsia. Of course, if we have an enlargement of the liver, we think first of alcoholism, and then of cholelithiasis and cholangitis. If we can exclude these, we may think of tuberculosis, carcinoma and syphilis. Personally, I have encountered enlargements and indurations of the liver of a temporary nature, in the course of colitis or gastritis, which disappeared when these conditions were cured. These hepatic enlargements could not be attributed to any of the other causes mentioned. Bouchard asserts that he has found enlargements of the liver in 23 per cent. of all his cases of dilatation of the stomach. My personal experience is that I do find hepatic enlargement with dilated stomachs, but not as frequently as Bouchard asserts. I should say, perhaps, in 10 per cent. of the cases. This so-called "liver of the dyspeptic" shows remarkable variation in size, under the influence of diet, and cleansing of the gastro-intestinal canal. For instance, a carefully sterilized diet, such as boiled milk and boiled beef, together with lavage of the colon and stomach, with bodily and mental rest, will very often cause a reduction in size. Roix has shown that lactic, butyric and acetic acid, when fed to experimental animals for a long time, may lead to a genuine cirrhosis of the liver. These acids

are among the most common and frequent results of abnormal gastro-intestinal digestion, and I see no reason why they should not cause hepatic irritation with consequent hyperemia in human beings, if they are compelled to pass through the liver parenchyma for years. The dyspeptic liver is, in my experience, not a frequent disease. It is not important because of its frequency, but it is most interesting that such a dyspeptic hepatic enlargement should occur at all. For instance, in sixty-four cases of hepatic cirrhosis, only four could not be attributed to the other causes before mentioned. Hanot and Boix attribute this hepatic enlargement to chronic intestinal auto-intoxication. It is a well-known fact that the liver is drawn into sympathetic affection in all intestinal infections and intoxications. There is an acute yellow atrophy of the liver which results from sausage poisoning, and there is an epidemic icterus of gastric-intestinal origin; then we have the so-called Weil's disease, which, as far as we understand it at present, is a febrile icterus in combination with hepatitis, which may run its course with severe disturbances of the central nervous system and terminate fatally. The liver changes may be due to toxic influences, because bacteria have not been found in the organ in many such conditions. Czerny and Thiemich have called attention to the frequent occurrence of fatty liver in association with gastro-intestinal catarrhs of children, but as this fatty liver may occur in any of the wasting diseases, it is doubtful whether it can be attributed to intestinal auto-intoxication.

Schiff, Heger and Rogers have called attention to the protecting function of the liver, by which it converts toxalbumins and other toxins into harmless substances. Nencki and his school confirmed this by experiments on exclusion of the liver from the circulation, after which toxic symptoms were caused, especially after albuminous

foods were ingested. Rovighi says: "Like unto Minos in Dante, the liver tests the conscience of those that want to enter and knows their sins."

CAN CHRONIC CONSTIPATION CAUSE INTESTINAL AUTO-INTOXICATION?—This is a much disputed point. In a very large number of cases of chronic constipation which I have carefully studied with regard to this question, I have not found a single case in which symptoms of auto-intoxication could be assigned to this condition, pure and simple. It is not plausible to assume that a condition which solidifies and condenses the fecal matter should predispose to constipation, but when constipation co-exists with diarrhea or where the hardened fecal matter exerts such an irritating effect upon the intestinal mucosa that enteritis and colitis are set up, in circumscribed areas at least, then we have more reasonable grounds for assuming self-poisoning. Bouchard ("Les Auto-intoxications," p. 165) regards constipation as a protection against auto-intoxication. He presumes that all that can be absorbed has been absorbed. Albu ("Ueber die Auto-Intoxicationen," etc.), who is otherwise an enthusiastic supporter of the new theory, is doubtful whether the consequences of chronic obstipation can be attributed to auto-intoxication. A similar view is held by Illoway ("Constipation in Adults and Children," p. 175). On the other hand, Friedrich Miller, "Intoxicationen Intestinalen Ursprunges," *Verhand. XVI Inner. Med.*, p. 165), who gives a very scholarly criticism of the modern literature on intestinal auto-intoxication, seems inclined to believe that the neurotic symptoms which sometimes accompany constipation are due to auto-intoxication, his main argument being that the headache and neurasthenic condition can be relieved by a laxative. At the same time, he gives a most logical analysis of the reflexes which may emanate from the gastro-intestinal tract (*l. c.*, p. 168), and even refers to the experiment of Beaumont

which I have just recalled. From his own logic I would preferably conclude that the nervous accompaniments of obstipation are of reflex origin.

There is no sound logic or objective proof thus far offered in medical literature to justify our assuming that chronic constipation may cause intestinal auto-intoxication.

TYPE OF INTERNAL AUTO-INTOXICATION.—An interesting group of acute attacks is frequently met with in the literature of this subject, and represented as a type of intestinal auto-intoxication. These cases are described as presenting the following symptoms: Stormy gastro-intestinal peristalsis, with vomiting and diarrhea or in some rare cases constipation, enteralgia, tympanites, coated tongue, headache, obscured consciousness, occasionally urticaria and erythema. Sometimes there is fever. Even slight icterus and albuminuria are reported in connection with this clinical picture, which resembles that following the ingestion of decayed or poisoned food. Such cases have been very unsatisfactorily described hitherto. Above all things we need exact clinical descriptions for such groups of symptoms before we are capable to classify them. It is not even possible to decide whether they are due to infections or to auto-intoxications.

It is a well-known experience that it requires a much more thorough elaboration to eradicate an error that has once taken hold of the medical profession than to spread a new hypothesis. The higher up in the air a theory is the more difficult it is to disprove. This can be said of the assertions which assign rachitis, leukemia, many skin, nervous and muscular diseases, to auto-intoxications.

CLASSIFICATION.—A satisfactory classification of the various forms of auto-intoxication is not practical in the present state of our knowledge. Von Jaksch classifies them into: (1) *Retention intoxications*, caused by the accumulation of physiological pro-

ducts of metabolism in consequence of closure or insufficiency of any one path of excretion; (2) *Noso-intoxications*, caused by pathological processes which alter the normal course of metabolism in such a way as to produce harmful in place of harmless products. Under this group von Jaksch ("Wien. klin. Wochenschr.," 1890, No. 52) distinguishes (a) diseases produced by disturbances of metabolism caused spontaneously in the organism, and (b) diseases caused by metabolic products of bacteria; (3) *Auto-intoxications caused by the effect of normal substances in large quantities*, which, however, are poisonous, or of poisonous substances which have originated from normal products. It is evident in this scheme that the auto-intoxications for which von Jaksch establishes a separate class are logically comprised in the second class, called *noso-intoxications*. For didactic reasons Albu ("Auto-Intoxicationen des Intestinal-Tractus," Berlin, 1895, S. 7) classifies these conditions into four groups: (1) Auto-intoxications caused by *loss of function of an organ*; these are generally glandular diseases, with or without anatomical changes. This group comprises myxedema, the strumous cachexia, pancreatic diabetes, acute yellow atrophy of the liver, and Addison's disease, which is supposed to originate in some form of atrophy of the adrenal bodies. They are diseases, then, caused by exclusion or loss of function of those organs to which the newer physiology attributes a destructive power of toxic metabolic products originating in the organism; (2) auto-intoxication by *general abnormalities of metabolism* without any evident localization. To this class belong the diseases in which the intermediate products of metabolism and the products of regressive metamorphosis reach the circulation; for instance, diabetes, gout, oxaluria; (3) auto-intoxication by *retention of physiological products of metabolism* in the various organs; for instance, toxic phenomena after

extensive skin burns, carbon dioxide poisoning when normal respiration is interfered with and uremia; (4) auto-intoxications caused by *overproduction of physiological and pathological products* of the organism—acetonuria, diaceturia, hydrothionemia, ammonemia, cystinuria and diabetic and carcinomatous coma.

The incoxications originating in the intestinal tract belong to both groups (3) and (4). They are observed in various stages of acute and chronic digestive disorders; in ileus, incarcerations and strangulations; in fact, all the obstructions; in the forms of intestinal dystrypsia or indigestion, etc.

DIAGNOSIS.—The diagnosis of a disease rests upon three factors, as a rule: (1) The symptoms or the clinical picture; (2) the physical signs, and (3) the results of chemic or microscopic examinations of the secretions and excretions, blood, stomach contents, feces, urine, sweat, etc.

(1) *The symptoms*.—The symptoms, which are most frequently observed in the beginning of auto-intoxication, are disturbances of gastro-intestinal peristalsis, vomiting and diarrhea in the acute cases; in others, constipation, enteralgia, abdominal distention, coated tongue, headache, obscured consciousness, occasionally urticaria and erythema. Among the chronic conditions which have been classed as intestinal auto-intoxication, the ammonemia, the hydrothionemia, the cystinuria, oxaluria, alcaptonuria, the symptoms will be those of these conditions, that is, if they produce symptoms at all. As a matter of fact, some of these states, particularly alcaptonuria, may exist without giving rise to symptoms. So much is evident. The clinical picture that has been given for intestinal auto-intoxication varies so extensively that it is impossible to make the diagnosis from the symptoms alone.

(2) *Physical signs*.—The physical signs which have been ascribed to intestinal auto-



intoxication are even more variable than the symptoms. Thus we have disturbances of vision, varying from asthenopia to absolute blindness. Cardiac signs expressing themselves in irregularities of the pulse. The pulse may be very fast or very slow; it may be weak or of increased tonicity. The reflexes may be preserved, much impeded or absent entirely. Thus Ewald reports the case of a man thirty-two years old who was brought to the hospital in a soporous condition, with the diagnosis of paraplegia. Two days after he was in the hospital he recovered consciousness, he stated that two to four days before the attack he had been quite well. He took a glass of Hunjadi Janos water to relieve constipation. After this he promptly became sick and began to vomit offensive brownish masses; pains began to be felt; he became apathetic and too feeble to move and to answer to questions. Pulse was so weak that ether and camphor injections had to be given every hour in the night after his admission to the hospital. His former weight was 138 pounds, his present weight 98 pounds; the pulse was so weak it could not be counted; pupillary reflex present, patellar reflex absent. Considerable quantities of a brownish decomposed fluid were evacuated from the stomach by means of the tube, and Ewald diagnosed an advanced gastric dilatation. Patient was admitted to the hospital April 3, 1895, but under lavage of the stomach and diet he was so much improved by the 6th of April that he no longer fell over as he formerly did on being removed from bed. The vomiting ceased and evacuations occurred after irrigation of the colon. It should be mentioned that in the offensive fluid which was evacuated on the first day of his admission by the stomach tube, there was no hydrochloric nor lactic acid; but the acidity after the test-meal, which was given on the fourth day, showed free HCL. equal 30 c. c. decinormal solution of NaOH; no lactic acid. Under continued lavage of the

stomach and colon, the patient improved so much in two weeks that he regained possession of his mental and bodily forces; only he could not recall what happened to him in the period immediately preceding his reception into the hospital. No tumor or enlarged glands were ever found in this patient, who was dismissed cured after fourteen days of treatment.

This clinical history is given with such detail because it represents, in Ewald's opinion, the type of grave auto-intoxication emanating from the stomach. A second type, which is presented by Ewald (*Verhandlungen des XVI Congress f. innere Med.*, 1898, p. 187) represents the auto-intoxication as it arises from the intestine. This patient, a woman fifty-two years old, had been admitted to the hospital under the diagnosis cerebral syphilis. There were no exanthemata, no swelling of the glands; she had gone through eight births, but had never miscarried. What had excited the suspicion of syphilis was the absence of a uvula, but it was elicited that the uvula had been lost under treatment by a physician who had cauterized a little white spot upon it with nitric acid. The uvula became ulcerated and dropped off. The patient was admitted in a comatose condition, with a history that for fourteen days she had vomited everything she had eaten; consciousness was clouded; she complained of headache, vertigo and stiffness of the muscles in the back of the neck. For twelve days preceding the admission into the hospital, the patient had had no evacuation of the bowels. The urine contained a large amount of indican; showed the Rosenbach reaction, but contained no acetone or diacetic acid. No tumor nor abnormality could be discovered on palpation. It was necessary to give a small injection of morphine in order to make her retain an Ewald test-breakfast. The test-meal showed free HCl and a total acidity of 42. Efforts were made to evacuate the bowels by high irrigations of water and



solutions containing purgative substances. For several days these efforts were futile. On the tenth day a stool was effected by a strong dose of a mixture of croton and castor oil. The stool was black as pitch and contained bismuth crystals. The patient asserted she had not taken bismuth except fourteen days prior to her admission. It was concluded that this bismuth had remained in the intestine almost four weeks. After this evacuation the patient rapidly improved, spontaneous bowel evacuations occurred, she had no more attacks of vertigo, etc., and after fourteen days she was discharged cured.

These are what Ewald designates as types of gastric and intestinal auto-intoxication. I have personally observed such cases and also patients in whom such attacks did not occur once only, but the coma, etc., together with the toxic gastro-intestinal symptoms, occurred three to four times in one year. But even in these two typical cases there is no proof offered for the compulsory acceptance of auto-intoxication. Particularly not in the second case, that of the woman with the prolonged obstipation; and as far as the objective demonstration of a toxine in the urine is concerned, Ewald admits that the gold salt of a Diamine, which he gained from the urine of similar cases, had no toxic effect upon animals. This question of excretion of toxins in the urine, brings us to the third means of diagnosis.

(3) *The results of chemic or microscopic examination of the secretions and excretions, blood, stomach contents, feces, urine, sweat, etc.*—It was an assertion of the school of Bouchard that normal urine contained a uro-toxine. The amount of urine which was necessary to kill a guinea pig, after it was injected into the veins of the animal, was taken by Bouchard to indicate the degree of toxicity.

URO-TOXIC CO-EFFICIENT OF BOUCHARD. —Four factors are taken into consideration to determine this co-efficient: (1) The

figure expressing in kilos the body weight of the person from whom the twenty-four hours collection of urine is taken; (2) the weight of the animal to be experimented upon in kilos; (3) the quantity of urine passed in twenty-four hours; (4) the amount of this urine necessary to kill the animal, when injected into the veins. The relation of the weight of the animal (in kilos), which is killed by a definite amount of urine, calculated to the kilo of body weight of the person from whom the urine is taken, represents the uro-toxic co-efficient. This is supposed to represent the toxicity of the urine necessary to kill a kilogram of living animal. In healthy human beings the average uro-toxic co-efficient is represented by the figure 0.465, and in diseases it varies from 0.1 to 2.0. The toxicity of the urine is, of course, dependent upon its concentration; but the uro-toxic co-efficient of Bouchard is a very problematic factor, on account of the difficulty of the technique it is impossible to apply the method clinically, and even in those instances in which it was applied and by capable clinical chemists, the practical deduction did not justify the amount of labor involved in the test.

In the discussion on intestinal auto-intoxication during the symposium on this subject at the XVI Congress f. innere Medicine (1. c., p. 201) Boas emphasized that it was a wonderful phenomenon that auto-intoxications did not manifest themselves during the occlusions and stenoses of the intestinal tract. He considered it remarkable that auto-intoxication had never been recorded in the large material of intestinal stenoses at the various clinics. But in the intestinal obstructions the absorption is rapidly paralyzed. (See Hergewater, Dis of Intestines, Vota.) In this connection I think it of interest to recall the experiments of Gulewitsch, according to which cholin may be transformed into neurin and muscarin in the intestinal canal, under certain condi-

tions. Cholin may pre-exist in the food, or it may be developed from lecithin, which is contained in eggs. Nesbitt (*Journal Experimental Med.*, Vol. iv, No. 1) has given the experimental evidence that cholin and neurin may be developed during intestinal occlusion, provided the food taken contains lecithin. Neurin may be formed from cholin by the action of bacteria. Among the toxic actions of neurin are a paralysis of the heart and increase of intestinal peristalsis. The practical deduction from these experiments is that eggs should be excluded from the diet in intestinal stenoses and occlusions, and that prior to the surgical operation, which may be necessary, the stomach and as much of the intestine as possible should be cleaned out by lavage. A diagnostic aid is also received from this work, for if neurin and cholin can be found in the intestinal contents, in cases of gradual intestinal stenosis, this should clinch the diagnosis and call for prompt treatment.

Although Frerichs has proven the harmlessness of acetone and acetic acid, Penzoldt and von Jaksch were of the opinion that these substances were poisonous when they were inhaled. The technic of these inhalation experiments has been criticised by Brieger, however.

The most fruitful analyst with regards to the isolation of ptomaines from the urine is Griffiths, according to whom (see Brieger, *Verhand. XVI Congress f. innere Med.*, p. 179) the urine of cases of pleurisy contains a toxine designated by him pleuricin; in eczema he finds eczemin; in carcinoma a carcinine; in epilepsy he finds a specific poisonous base; in angina pectoris a poisonous leucomain; in croup a propyl glycocycin; in scarlatina and influenza he finds poisonous and fever-producing bases. A scientific confirmation of this work is absolutely necessary.

**TOXICITY OF THE SWEAT.** — Arloing found that the injection of from 15 to 25 per cent. of sweat per kilogram of the ani-

mal would cause death. Charin and Mavrojanis observed increased temperature, prostration hematuria and death occur after the injection of 60 ccm. But Brieger (l. c., p. 180) and Davidson found that the injection of 60 and more ccm. of sweat gained after sweat bath did not cause the death of guinea pig. These latter observers, however, sterilized the sweat by freeing it from bacteria, by means of the Pukall filter, so that the effect produced by previous experimenters must be attributed to bacteria.

**TOXICITY OF THE BLOOD.**—This has been investigated recently by Uhlenhut (*Zeitschr. f. Hygiene u. Infectionens Krankheiten*). His chief results are the following: (1) Intravenous injection of serum into guinea pigs does not permit of exact deductions; (2) sub-cutaneous injection of blood serum into guinea pigs is apparently available for logical deductions; (3) the normal blood serum of man, sheep, pig, rabbit, even in very small doses (0.5 ccm.) when injected hypodermically into guinea pigs, causes infiltrates, and in large doses necrosis. The injection of 20 ccm. of any of these serums causes death of the guinea pig. Normal horse serum produces no infiltrates until a dose of 20 ccm. is reached, when small infiltrates appear, which are rapidly absorbed; (4) the blood serum of four scarlet fever and two typhoid fever patients was toxic in very minute doses; (5) the serum of scarlet fever caused clouded swelling of the kidneys, with partial fatty metamorphosis, a change which could not be produced by the typhoid fever serum. Whether it could be caused by normal blood serum or not was not ascertained. These toxins of blood serum cannot be removed by filtration through a Pasteur filter; they seem to belong to the class of toxalbumins.

From a chemical standpoint the toxins which occur in feces, urine, sweat, blood, etc., are classified as crystallizable toxins, and non crystallizable or amorphous toxins. The latter have been designated by

Frank Brieger and Frankel as tox-albumins. It was at one time thought that they were of an albuminous character.\*

It appears that of the two groups, the crystallizable and the amorphous toxins, the latter, i. e., the tox-albumins, are the most important. It appears also that they are not albuminous bodies but toxins intimately attached or combined with albuminous bodies. They are poisons which can be separated from the organic albumin of the body only with great difficulty, and are extremely decomposable. These substances are so extremely poisonous that their toxicity surpasses comprehension, but still it can be demonstrated by experiment. In order to obtain a sufficient quantity of these substances for the purposes of weighing them, hundreds of liters of culture bouillon or hundreds of kilos of human feces are necessary. These poisons are destroyed by acids, even the weakest, and preserved by alkalis. Curiously enough, the same properties are possessed by the so-called anti-toxins. We should, therefore, not conceive of the antagonistic physiologic action of toxin and anti-toxin as being comparable to neutralization. The amorphous toxins, or toxalbumins, may, in some instances, produce the typical clinical picture of the disease, in the course of which they are found in the blood. These toxalbumins have, in certain conditions of auto-intoxication, in tetanus, sausage-poisoning (botulismus) and diphtheria, been isolated from the blood, and the fact that after isolation they may produce the identical clinical picture characteristic of the original disease on being injected into other animals, constitutes the strongest evidence for the theory of auto-intoxication.

\* I have repeatedly stated in the course of this article that the chemic and physiologic relations of the subject of intestinal auto-intoxication calls for careful and critical testing. The technical difficulties of analyses, frequently baffle the most experienced physiologic chemist.

In the experiments of the effect of the blood serum of animals of one species upon the organism of the animals of another species, the experimenters have attributed toxic phenomena to the serum when the deleterious results observed could, with as much justification, be attributed to differences in *osmotic tension*. When solutions of different concentrations meet in the circulation of the animal organism, changes occur which at once act detrimentally upon the tissue juices. These changes have been designated as osmotic tension. The transference of the blood of a male animal into the circulation of a female animal of the same species may even cause such phenomena.

The whole subject of the diagnosis of intestinal auto-intoxication is at present in such a chaotic state that clinicians with analytical minds will be extremely conservative in making the diagnosis at all. The evidences to be derived from examination of the secretions and excretions, the blood, etc., require such experience in chemic and physiologic technic as to be unavailable for clinical purposes. The physical signs may be absent, and the symptomatology so variable that the diagnosis will rarely go beyond a tentative or suggestive one. In none of the diseases which have been ascribed to intestinal auto-intoxication are we absolutely compelled by the logic of all the chemic, pathologic and symptomatologic factors entering into the cases to accept the view that the organism has been poisoned from the stomach and intestines. I do not wish to deny that this may be and really is the case in many instances, but I only wish to emphasize that the uncontrovertible objective proof of this assumption has as yet not been furnished.

TREATMENT.—In some instances the practitioner may decide, after careful consideration of the case, that a process of self-poisoning from the gastro-intestinal tract, is a complicating factor. If the treatment instituted to prevent the flooding of the



system with toxins results in improvement, it is usually taken as a confirmation of the tentative diagnosis of auto-intoxication. This is not always a logical deduction, for relief may follow when the symptoms were not due to self poisoning, but due to reflexes. The prompt improvement following on thorough evacuation of the intestinal canal after obstipation does not prove satisfactorily that self-poisoning had existed; the symptoms may have been reflexes.

The old theory of the reflexes of course is not applicable in explanation of such conditions as diabetic coma, uremia, carcinomatous coma, etc., but it may explain such states as gastric and intestinal vertigo, and dyspeptic asthma. The experiment of Beaumont, on the stomach of Alexis St. Martin by causing vertigo and pallor of the face immediately after the stomach was touched with a thermometer is the time honored physiologic evidence of what a reflex from the stomach may produce. The so-called "dyspeptic asthma," which is in the main a cardiac dyspnea, has been described as occurring in association with overloading of the stomach with indigestible food. I have observed three cases of this condition. They occurred so promptly after a meal that there could be no possibility of decomposition of the ingesta. The symptoms ceased at once, as soon as vomiting had emptied the stomach of ingesta, which upon analysis were not found decomposed. It is therefore improbable that an auto-intoxication could be at the bottom of dyspeptic asthma; it is more likely to be due to a reflex. An interesting polemic has taken place between Katz (*Weiner Med. Presse*, 1893, No. 28) Albu (*Auto-intoxicationen*, p. 200), and Müller (*Verhandl. d. XVI Congress f. innere Med.*, p. 168), as to how far the old reflex theory will suffice in explaining phenomena that are claimed to be due to auto-intoxication. Katz maintains that the reflex will explain the majority of these

symptoms, Albu will give very little room to the old theory, rather favoring the modern view of intestinal auto-intoxication, whilst Müller occupies an intermediate position. The whole polemic has, however, not been very productive in clearing up the subject, as Albu himself finally admits "It still remains the work of the future to sift out those cases in which the reflex and those in which the auto-intoxication is the cause of the disease." This entire polemic reminds me of an amusing verse which I found in an old medical treatise:

Der Erste hat ein Haar gespalten  
Und einen Vortrag darüber gehalten,  
Der Zweite fügt es wieder zusammen  
Und muss die Ansicht des Ersten verdammen;  
Im Buch des Dritten ist zu lesen,  
Es sei nicht das richtige Haar gewesen.

which in English would read about as follows:

The first one, had split a hair  
And lectured on it everywhere,  
The second, put it together again  
And swore the work of the first was in vain;  
In the book of the third you may read  
That it was not the right hair indeed.

The methods of treatment may be arranged as follows: (1) The diet; (2) Lavage of the stomach, of the colon and rectum, and enteroclysis; (3) Treatment by medicines, purges and emetics; (4) Intestinal antiseptics; (5) Specific medication (Brewer's yeast, menthol, ichthyol, hydrochloric acid, calomel, etc.); (6) Methods directed to increasing elimination by the skin; (7) By kidneys; (8) Elimination of toxins by the infusion of normal salt solutions; (9) Venesection.

(1) *Diet*. In the following the usefulness of the various means of treatment will be considered independently of any theory attempting an explanation of their action. We often know what relieves certain symptoms of self poisoning, and yet we do not know how the agent acts. In this condition, more than in any other disease to which the human frame is sub-



ject, individualization is most important. It is this individualization which distinguishes the trained physician from the "quack" who is a "routinier" who does not deviate from his scheme, and attempts to apply his stereotyped, castiron practices to all patients alike. The trained physician, however, is a man with an analytical mind, who treats the patient, not the disease—who treats the individual, whilst at the same time he has eye to the underlying pathogenic factors.

**TEMPORARY TOTAL ABSTENTION FROM FOOD.**—In the acute gastro-intestinal auto-intoxications a patient who takes no food is not really starving, he is only, for the time being, living on his own fat stored up in the body, and on the glycogen stored up in the liver. There is an "interstitial digestion," as Claude Bernard calls it, in which no toxins are generated. By cutting off the food from the digestive tract we are taking the wind out of the sails of the microscopic demons who are setting up a revolution in the intestines. In acute intoxications nature itself points out the expediency of total abstinence from food, for such patients, having rather a disgust than an appetite for food, and refuse to partake of any diet. But in chronic auto-intoxications the conditions are different. Here a carefully selected diet and one adapted to the individuality of the case is necessary.

**DIET FOR CHRONIC AUTO-INTOXICATION.** There can be no doubt that decided benefit to the patient can result from a methodical control of the diet. This has been shown by Escherich in the intestinal auto-intoxications of children. In a general way it may be said that in these conditions, at least, the putrefaction of proteids or albuminous food becomes arrested by a predominating fermentation of the carbohydrates. Secondly, it can be asserted in a general way that the processes of decomposition are dependent upon the character of the food. For instance, a so-

called acid dyspepsia which depended upon fermentation of milk can be arrested by exclusive dieting with egg albumen; and again, an albumin putrefaction can be checked by a diet of farinaceous food. Above all things, it is necessary to find out the particular article of diet which is undergoing decomposition. This can be discovered by a careful study of the feces, particularly with the aid of the Boas stool sieve (see Hemmeter's "Diseases of the Intestines, Vol. I"). The article of diet which is indigestible, will, as a rule, be caught upon the sieve, and can easily be recognized.

In this connection a study of the personal diet idiosyncracies is of great interest. Some persons cannot eat strawberries without suffering from intense urticaria, others will have intestinal auto-intoxication from eating crab or fish eggs, too much sugar, etc.

**THE ABDOMINAL BRAIN.**—In this connection, with the diet idiosyncracies, I cannot resist narrating an opinion of the celebrated Leipzig physiologist, Ludwig. A certain article of diet was forbidden to him during an attack of sickness, whereupon he answered, "That I will digest perfectly well, the intestine has its own brain, it functions differently in different people; just as the cerebrum disposes and qualifies one man to become a merchant and another man to become an artist, similarly my intestinal brain is so adjusted that I can digest cranberries and cucumbers, whilst another person's intestines cannot." This characteristic of the abdominal or intestinal brain, as Ludwig called it, makes it intelligible to us why certain people have idiosyncracies to certain articles of diet. It happens sometimes that an adult may digest a certain food perfectly, until one day, by an exceptional coincidence of circumstances, such as mental and physical overwork, nervous excitement and catching cold, he will be in a condition where this food, which he has always digested

perfectly, will give rise to toxic phenomena. Curiously enough this diet substance may from now on act as a poison for many years, perhaps for life. Some change has occurred in the abdominal brain whereby it will always remember that mischievous article and begin to resent its admission to the organism the minute it reaches the digestive tract.

**FATAL EFFECTS OF CERTAIN DIET COMBINATIONS IN ANIMALS.**—This subject has a certain experimental basis which will serve to impress upon the general practitioner the great importance of individualization in diet, for it would no doubt interest him to know that in certain animals death can be caused by definite combinations in diet. For example: It is a well known fact that rabbits can digest grape sugar perfectly well. An ordinary rabbit can tolerate 50 to 60 grains of glucose and only traces of it appear in the urine. The remaining diet, during this glucose feeding, must consist of green vegetables, carrots or turnips. If, after this, the animals are put upon a diet of oats, during which the urine becomes very acid, and they are given glucose in very few minutes after this same sugar is taken the animals will become weak and die within a few hours. Cane sugar and glucose will have the same effect; but milk sugar, in addition to feeding of oats, will produce no such toxic effects. Here is an instance of a fatal effect produced in an animal by exceptional combination of otherwise harmless dietetic articles. It should be added that if calcium carbonate was added to the oats, the toxic phenomena did not appear in these rabbits. That a combination of glucose and oats is not fatal to all herbivorous animals requires no confirmation. Personally, I have frequently fed my saddle horse with dextrose after he had eaten a hearty meal of oats, and he seemed to thrive upon the combination. The experiment of the rabbit is valuable simply in suggesting the

different construction and functioning of the digestive process in these rodents.

There are three ways of ascertaining, by laboratory methods, whether any particular food has an influence on reducing auto-intoxication. The first is the determination of the ethereal sulphates in the urine, and the second is the determination of the number of bacteria in a weighed amount of the feces; the third is the fermentation of the feces in graduated fermentation tubes, as originally practiced by Adolph Schmidt (*"Die Fæces des Menschen im normalen und krankhaften Zustande,"* I. Theil). Unfortunately none of these methods are exact. The determination of the ethereal sulphates involves time-robbing analyses and the normal variations in the quantity of the performed and conjugate sulphates are so great that any deduction made from such analyses should be drawn with great conservatism. The counting of the bacteria in weighed amounts of feces is also a very time-robbing and variable method, and the practical deductions of the feces (see Hemmelter's *"Diseases of the Intestines,"* Vol. I, p. 248), if it gives positive reactions, that is, if the fermentation tube is filled during the first twenty-four hours, when there are no other symptoms of intestinal disturbance, in my experience it signifies that the carbohydrates are not digested perfectly. There is an early and a late fermentation. The late fermentation begins on the second or third day, and forms gases consisting largely of marsh gas and hydrogen sulphide, whereas the early fermentation produces 75 per cent. carbon dioxid. This method of Schmidt has been much criticised by Basch and Kersberger, nevertheless, in my opinion, if the method be consistently practiced after exactly known diets, it is of a certain utility in determining the degree of starch indigestion. After a diet consisting of a quart of milk, four eggs, three pieces of toast, a plate of oat meal soup, and a plate of flour soup, one cup of bouil-

lon and 120 grams of potato, there should normally be no fermentation in the first twenty-four hours. If it does occur it means there is an imperfect digestion of the starches. This can much more rapidly be found by micro and monoscopic examination of the feces, however.

In cases where milk has formerly been well digested, this substance constitutes the dietetic antiseptic "par excellence." In cities and in the country pasteurized milk should be preferred in all cases. This milk has been subjected to sufficient temperature to destroy the possible infectious bacteria, the tubercle, typhoid, diphtheria, cholera and influenza bacilli. Sterilized milk has been subjected to a much higher temperature for three successive periods. The temperature is raised to 110 or 115 degrees C. Unfortunately such milk, whilst it may be absolutely free of bacteria, it is decidedly more difficult to digest than milk which has been only pasteurized, or that which has not been boiled at all. According to Müller, (l. c.) it has recently been asserted that rachitis is the result of excessively sterilized diet for children. This does not harmonize with the theory of Combi, according to which this disease is a consequence of intestinal auto-intoxication. There should be no difficulty to obtain milk in the larger cities which is practically so free from bacteria that very slight pasteurization will suffice to render it a safe and useful article of diet in intestinal auto-intoxication. It should not be forgotten that rennin or chymosin, the milk curdling ferment of the human stomach, will curdle raw milk seven to eight times as rapidly as it will sterilized milk, and that raw milk is much easier digested and absorbed than even pasteurized milk.

(2) *Lavage of the Stomach, Colon and Rectum, and Enteroclysis.*—The only genuine intestinal antiseptic is evacuation of the digestive tract. Many times the patient himself will have made the first efforts to accomplish this result. But where vomiting

and purging have not yet taken place, or where it has been kept up an unduly long time, lavage of the stomach and of the colon should be at once undertaken. Enteroclysis, which means the attempt to force water through the entire large and small intestines, even if it were possible, is not necessary, because a thorough cleansing out of the colon and stomach by irrigation has proven sufficient. This gastric and colon lavage is the one therapeutic measure concerning the utility of which there are no dissenting opinions.

(3) *Treatment by Purges and Emetics.*—Where lavage of the stomach and colon are practiced, emetics and purges are unnecessary, but if instruments are not at hand for washing out the digestive tract, such drugs can be used. The most practical emetic is the following:

℞ Powdered ipecac,	20
Antimonium and potassium tartate	5.6

Take at once.

Apomorphine hydrochlorate, in doses of 1-12 grain hypodermically is too depressive to use in the majority of cases of auto-intoxication. Personally, I have never been compelled to resort to it. The best purges are calomel and castor oil. It will hardly be necessary to specify their mode of administration.

(4) *Intestinal Antiseptics.*—The human intestine is provided with a natural means of defense against the bacteria. This normal provision for intestinal disinfection is often injured by the very means we use to destroy the intestinal bacteria. A similar natural protective provision against bacteria infection exists in the vagina. Obstetricians have recognized that this provision can be injured by antiseptic vaginal irrigations. R. Schütz (Berliner klin. Wochshr, 1900, No. 25) has studied this natural means of defence against bacteria by means of administering counted numbers of the vibrio of Metschnikoff, and has discovered that whilst the intestine will get rid of enormous numbers of this organism



unaided, they will appear in the feces to a large extent if the normal peristalsis is interfered with by drugs. Even calomel caused the appearance of larger numbers of the vibrio of Metschnikoff than when no drug was given. This normal defence against bacterial aggression is much more developed in the lower animals, the dog for instance, which may explain the observation that intestinal auto-intoxications are unknown in animals (Fröhner, Veterinary Academy of Berlin). Antiseptics may do harm not only by destroying this intrinsic protection of the intestine, but the toxic properties of the antiseptics may reduce the resistance and the healing tendency of the living cells. Only such intestinal antiseptics should be considered which are not soluble and cannot be absorbed from the upper part of the digestive tract, and therefore stand some chance of reaching the lower intestinal districts where the putrefaction is most intense. For this purpose the following substances have been used: Derivatives of formaldehyde, calomel, menthol, enterocresol, veroform, iodoform, naphthaline, naphthol, turpentine, bismuth compounds, preparations of salicylic acid, salol, tannin, betanaphthol, etc. R. Stern (Verhandlungen d. XVI f. innere Medicine, p. 199) has studied the effect of a number of these substances mentioned, particularly calomel, salol and betanaphthol, upon known quantities of cultures of "Bacillus prodigiosus," which were introduced into the intestinal canal of animals. He found that the feces contained an abundance of these bacteria during the time that these antiseptics were used. I do not wish to characterize the attempts at intestinal antiseptics by these drugs as useless, for after all it is not the destruction of bacteria which should be aimed at, but simply their innocuousness. If we can weaken them sufficiently to prevent them from exerting their deleterious effects, auto-intoxication will not occur. The evidences that certain medications really

do benefit the patient even though there may be no evidences to this effect in the urine and stool, will be given in the next paragraph on specific medication. I had a personal experience which confirms this view. Following an attack of obstipation I suffered from rheumatism in the left arm, and headache. Ten grains of beta-uaphthol and ten grains of salicylate of bismuth were taken three times a day for a week, together with oil enemata. The amount of the ethereal sulphates in the urine did not decrease nor was there any diminution in the number of bacteria in a weighed amount of fecal matter, but the symptoms all disappeared and I recovered on the sixth day, and returned to my ordinary diet.

(5) *Special or Specific Medication*—There are certain remedies which seem to exert a special influence on special intestinal fermentation and putrefaction. Quinke (Verhandlungen d. XVI Congress f. innere Med., s. 193) claims to have observed great improvement in certain diarrheas and intestinal dyspepsias under the administration of brewer's yeast in pure culture, and Ageron (L. C., s. 195) asserted that Berlin Weiss beer, which contains large amounts of brewer's yeast, was very beneficial in cases of cholera that occurred in Hamburg. Brewer's yeast is a complex growth of bacteria and fungi, and has for some time been known to exert a beneficial effect in furunculosis, and it is supposed to act upon the principle of destroying one bacterium by another. Rosenheim observed an improved starch digestion in obstipation by use of this yeast. This "driving out of the devil by Beelzebub" is a questionable proceeding, and particularly in cases of advanced prostration and diarrhea it should not be employed. Another dietetic way of accomplishing this object is to permit the consumption of cheese, small quantities of Neufchatelle or Swiss cheese. It is possible that the bacteria contained in cheese are the pharmacologic basis.



Shakespeare was sensible to the attributes of cheese in the process of digestion, and alludes humorously to it in "Troilus and Cressida," (Act II, Scene 3) when he makes one of his characters exclaim, "Where, where! Art thou come? Why, my cheese, my digestion, why hast thou not served thyself in to my table so many meals."

Brewer's yeast has recently been brought upon the market in pure culture and a French house has made an extract of it under the name of "levurine." Brewer's yeast as such is a most disgusting substance, and will hardly be taken by any refined patient, whereas this class would possibly not object to eating Neufchatelle cheese and drinking "Weiss bier."

The other special medications with which I have experience are menthol and ichthyol, in urticaria depending upon strawberries, crab and fish indigestion; hydrochloric acid in cases of achylia gastrica, and whenever the gastric analysis shows the absence of free HCl. Salicylic acid in doses of eight grains, largely diluted, in gastric dilation with much distention and flatulence. Calomel in obese patients with enlarged livers. All of these remedies are of decided utility when given for these special indications.

(6) *Methods Directed to Increasing Elimination by the Skin.*—This effort is not always necessary, but if a patient taken with acute auto-intoxication is known to have uric acid diathesis, to have previously suffered from renal insufficiency or if the attack has been known to have come on after chilling of the surface, a sweat bath will frequently influence the situation favorably. Sweating should not be effected by internal medication, except perhaps hot teas, but rather by hot baths and hot external applications.

(7) *Efforts to Increase Elimination by the Kidneys.*—In all cases of supposed auto-intoxication it is indispensable that the

urine should be measured for twenty-four hours, in order to gain an adequate conception of the amount of urine passed. It has been my experience that the total amount of urine passed in twenty-four hours is as a rule very much reduced in most all genuine auto-intoxications, during the period of the intoxication. Sometimes a patient is seen immediately after the process of self-poisoning has improved. If the urine is measured at this stage it occasionally shows an increase above the normal for twenty-four hours; thus the total quantity may be 1800 to 2000 c.c. in twenty-four hours. This is to be looked upon as a reaction after the diminished secretion during the intoxication.

RENAL INSUFFICIENCY IN AUTO-INTOXICATION.—I have frequently observed that the amount of urine passed in twenty-four hours sinks to a minimum and at the same time the amount of solid substances contained in this small amount of urine is almost below the normal. Boas (XVI Congress f. i. M., p. 202) mentions the case of a lady in whom the total amount of twenty-four hours urine sank to 300 to 400 c.c., and had a very low specific gravity. All efforts to increase the amount of urine by abundant drinking of water and large enemata were futile. Personally, I believe that much practical information can be gained by simply measuring the urine of such patients and determining its specific gravity.

DETERMINATION OF THE AMOUNT OF SOLIDS IN THE URINE BY MEANS OF THE URINOMETER.—If the last two decimal points of the specific gravity of the urine are multiplied by 2.33, the product indicates in grammes the quantity of solid substances contained in 1000 c. c. of that urine. For the sake of cleanness and brevity I will multiply by 2, instead of 2.33. Supposing somebody had passed 1500 c. c. urine in twenty-four hours, and the specific gravity is 1015, multiplying the last two figures by 2, we get the following:

Fifteen by two equals 30 grammes solid substances in 1000 c. c of urine, therefore there are 15 grammes in 500 c. c., and 45 grammes in 1500 c. c. or the total quantity passed. It has been shown that about one-half of the solid substances of the urine are made up of urea, and one-fourth of chloride of sodium. Now, as we have 45 grammes of solid substances, one-half is 22.5 grammes which represents the amount of urea; and one-fourth is 11.25 grammes representing the amount of chlorid of sodium, and the balance, 11.25 grammes, would cover the remaining solid constituents. These figures obtained by multiplying with 2.33 are not absolutely correct, but I have found from a large number of quantitative analyses of the solid substances of the urine, that they are sufficiently approximate to acquire some conception of the amount of solids in the urine, as long as it is physiological urine. But when albumin and sugar are present in the urine, this way of determining the solid constituents by the specific gravity, becomes fallacious. But even here it is by no means to be disregarded as a quick method of determining the total urinary solids. We must have regard for methods available by the general practitioner who as a rule is not a chemist even if these methods are not exact. In order to increase the urinary secretion when it is suppressed, the mild diuretics should be tried first; the potassium and sodium tartrate and bicarbonate in doses of 10 to 20 grains. If there is decided enfeebled cardiac action, infusion of digitalis with acetate of potassium and tinct. of nuxvomica are advisable. Calomel is a good diuretic, and caffeine, together with strychnin has also a sphere of usefulness in these conditions. Diuretin is an available remedy. But no one would be justified in using any of these drugs unless he had determined beforehand, by measurement and ascertaining the total solids

through the specific gravity, that a renal insufficiency actually existed.

(8) *Elimination of Toxines by Infusion of Normal Salt Solutions.*—There is no more rapid way of increasing the amount of urine than the subcutaneous infusion of sterile normal salt solutions. It is particularly valuable in those acute intoxications where the circulation is depressed and the arterial pressure reduced. In intensely acute intoxications, which occur in the infectious fevers, these infusions are of undoubted value, in my experience. I believe that life has been saved by this procedure in two cases of very severe auto-intoxication occurring in the course of typhoid fever, in my practice. Where our object is to flush out toxines, there can be no more prompt or effective method of accomplishing it than this one. This method cannot be replaced by the drinking of water, or injecting it into the intestines, for many times there is vomiting and purging and even if these are not present, the gastro-intestinal tract may refuse to retain such considerable quantities of water.

(9) *Venesection (Blood Letting).*—There is no doubt that even this heroic method has its sphere of utility in cases where the circulation is loaded with toxic substances, especially in plethoric subjects, with high arterial tension. In one case of severe auto-intoxication due to compression of the intestines by adhesions emanating from the gall-bladder (proved to be such by subsequent operation) the patient was brought to the city from the country in an unconscious condition. The practitioner in charge had stated that unconsciousness had developed so suddenly that cerebral hemorrhage and apoplexy was suspected. He urged venesection, which was executed because he argued that it had restored the patient to consciousness on a previous occasion. About a pint and a half of blood was drawn by the prac-

itioner in charge, and the patient recovered about four hours later, at least he was in full possession of his mental faculties when I saw him about that time after the venesection. It was then possible to obtain a previous history of the patient, which pointed to cholelithiasis and obstruction. An operation completely relieved this patient. But the effect of the blood letting was so manifest that personally I was convinced that the restoration of consciousness was due to diminution of poisons by this step.

In conclusion I desire to emphasize that intestinal auto-intoxications are most effectively treated by prophylactic measures,

diet, evacuation of the gastro-intestinal canal, rest and restoring the digestive tract to normal functioning after an exact diagnosis has been established. The idea has been suggested that this form of intoxication, like the exogenous poisoning, might be treated by antitoxines, or antidotes. It is not impossible that we may in future come into possession of anti-toxines effective also against the poisons originating within the body, but in order to accomplish this we must first isolate these toxins, and study them outside of the organism. So far the idea of the antitoxic treatment of the auto-intoxications is nothing more than a brilliant suggestion.







Reprinted from the American Journal of Physiology.

VOL. XVII. — DECEMBER 1, 1906. — NO. IV.

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AN IMPROVED OPERATIVE METHOD OF FORMING AN  
EXPERIMENTAL ACCESSORY (PAWLOW) STOMACH  
IN THE DOG.

By JOHN C. HEMMETER.



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[*Baltimore.*]

IN his article on the Physiological Surgery of the Digestive Tract, J. P. Pawlow,<sup>1</sup> after considering the advantages and disadvantages of previous experiments upon the stomach, gives a description of two new operative methods. The main object of Pawlow's new operation is to secure gastric juice for physiological purposes by preparing an accessory stomach in such a way that the secretory fibres of the organ shall not be injured, that the juice can be obtained in a pure state, that is, without admixture of food, and yet the glandular apparatus be stimulated from the interior surface of the gastric mucosa as it is under normal conditions.

This operation has proved very difficult even in the hands of skilled abdominal surgeons, and when performed under perfect aseptic technique. The animals do not, as a rule, die from infection; they seem to die from the prolonged etherization. The object of the reporter was to devise an operation accomplishing the same purposes as that of Pawlow, and yet capable of a more rapid execution because of greater simplicity in plan. An incision is made almost along the same line as the original incision of Pawlow, but the object of this incision is not to divide the stomach into two parts, for it is only carried through the anterior wall of the stomach. (Pawlow's incision goes through the anterior and posterior wall.) The object of my incision is simply to enable the operator to push the mucosa of the stomach out through the line *AB* (Fig. 1) by invaginating the fundus or greater curvature through it. Next an incision is made only through the mucosa in a semicircular way, from the greater curvature at *C* to the greater curvature at *D*, going about as high as the lower third

<sup>1</sup> PAWLOW: *Ergebnisse der Physiologie*, Erster Jahrgang, 1 Abt. p. 258.



of the stomach, or one-third of the distance between the greater and lesser curvature, along the line *F E G* (Figs. 3 and 4). The

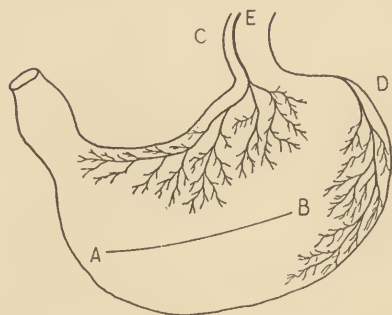


FIGURE 1.—*A B*, line of Pawlow first incision. *C*, vagus and anterior gastric plexus. *D*, vagus and posterior gastric plexus. *E*, esophagus.

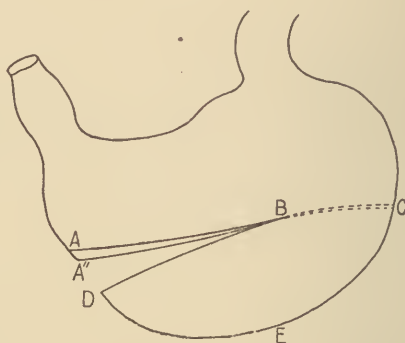


FIGURE 2.—Effect and appearance after first incision according to Pawlow. The lines *AB*, *A''B*, and *DB* are closed by sutures. The accessory stomach is made out of the part enclosed by letters *BC*, *DE*. The stomach is made into two compartments by sewing together two layers of mucosa after they are dissected loose—along the dotted line *BC*.

incision goes through the mucosa only; the mucosa then is very slightly dissected off on either side of the incision not more than is necessary in order to catch hold of it with the forceps, for the pur-



FIGURE 3. Pawlow's origin operation.—*A*, Line of sutures. *B*, abdominal wall. The dotted lines represent mucosa.

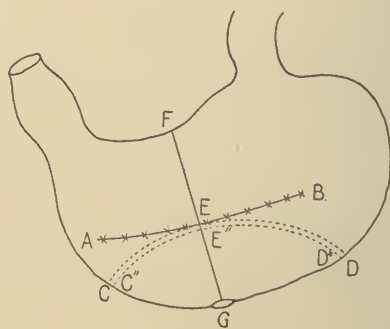


FIGURE 4.

pose of getting sutures through the cut ends of the mucosa. The incision is made both on the anterior and posterior walls of the stomach. As far as possible the incisions must be parallel to each other, so that when the semicircular incision on the anterior wall is approximated to that on the posterior wall of the stomach, they coincide exactly. These two incisions are next united by silk sutures beginning at the point *C* on the greater curvature, and making sure

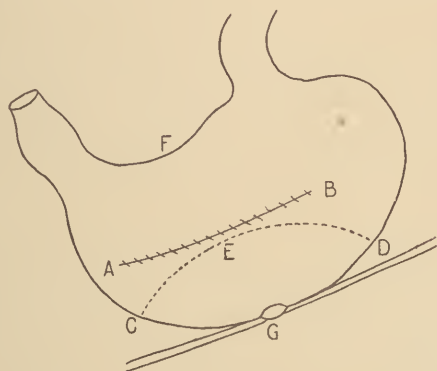


FIGURE 5. — *G*, fistula on anterior abdominal wall.

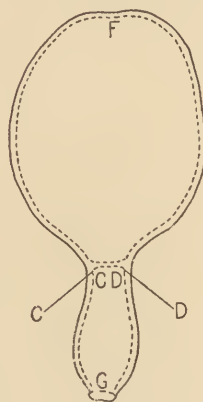


FIGURE 6.

that the angle of the pouch is tightly walled off from the greater part of the stomach by the sutures at this point *C*. The sutures are then carried along the semicircular incision from *C* to *E* to *D*. In this way the anterior and posterior walls are united by an inner row of silk sutures, which are inserted no deeper than the muscularis mucosæ. This has to be done by pushing the part of the greater curvature (*C E D* in Fig. 4) through the incision *A B*. When the anterior and posterior gastric walls are thus united along the lines *C E D* and *C' E' D'*, a circular pouch is formed (*C E D G*, in Fig. 4), separating this part of the stomach from the rest. Next the opening in the anterior gastric wall along the line *A B* is closed by sutures, a fistulous opening is made at *G*, and this point attached to the external abdominal wall as in Pawlow's method. On cross section of the stomach along the line *F G* (Fig. 4) the appearance of the main and accessory stomach when viewed from the fundus would be as represented in Fig. 6. The question might be asked, what becomes of that part of the large incision through the mucosa which faces the smaller or accessory stomach along *C* to *E* to *D* on

the inner side of the accessory stomach, because no mention has been made that this is closed by sutures. In most of my animals I have permitted it to take care of itself, for it heals within eight to ten days, as subsequent opening of the gastric cavity at this point has proved. The secretory fibres of the vagus are not injured in this operation, which is simpler of execution, requires less time than the Pawlow operation, and accomplishes all that this operation aims at.

A difficulty met with constantly in all animals thus operated on is the erosion and autodigestion of the skin around the abdominal opening. This untoward complication is due to the proteolytic effect of the gastric juice and to pressure by the rubber tube or cannula used to establish an outlet from the experimental accessory stomach. If the dog is permitted to lie down, there will be still larger erosions, because the abdominal integument comes to rest in a pool of escaped gastric juice.

Two things are of great assistance in this difficulty: one is the support of the animal by two broad bandages passed under the thorax anterior to the fistula and under the abdomen posterior to the same, fixing the dog to an upright holder so that he cannot lie down. The animal becomes reconciled to the holder and bandages in a few days and learns to rest and sleep in this fixture. If other animals are in the same room, the dog operated on must be blindfolded, because the secretion of gastric juice is notably influenced by psychic processes, caused by actions of the experimenter and the behavior of other animals.

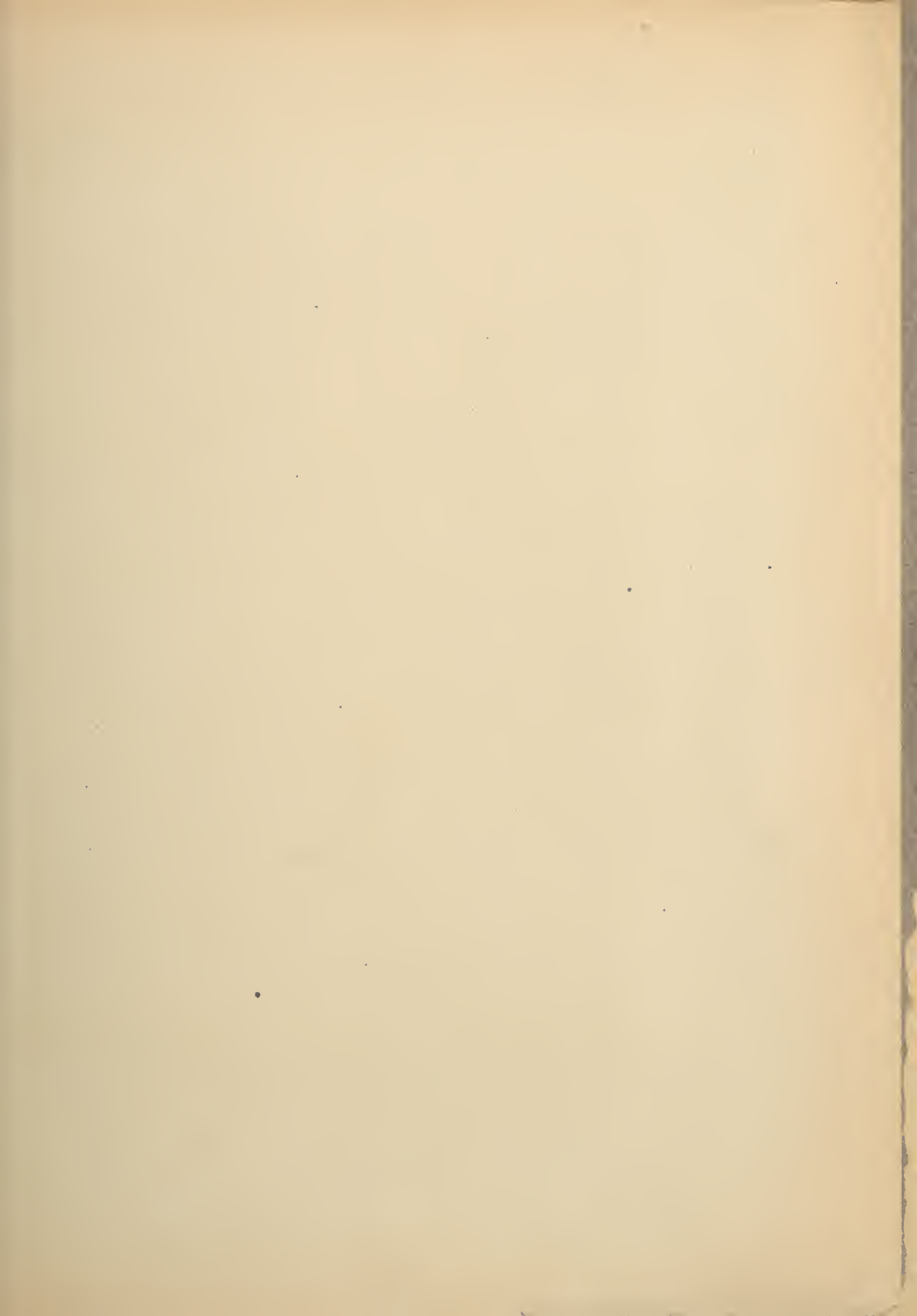
Another helpful factor is the dressing of the integument around the abdominal wound during the entire time in which the animal is under actual observation, that is, during the hours when juice is collected and even during the hours of rest. The main object of this dressing is to render the gastric juice inert and at the same time to protect the surface of the skin. After testing a number of substances as dressing powders I finally settled on simple zinc oxide made alkaline with sodium bicarbonate,—about one part of sodium bicarbonate to five parts of zinc oxide. During the hours of rest this powder is applied liberally all around the cannula or rubber discharge tube. But during the hours of collection of juice care must be had lest some of the alkaline powder fall into the collecting bottles and neutralize the juice. It had best be wiped off by a little absorbent cotton before the bottle is applied. While the juice is being collected it rarely spreads to the surrounding integu-

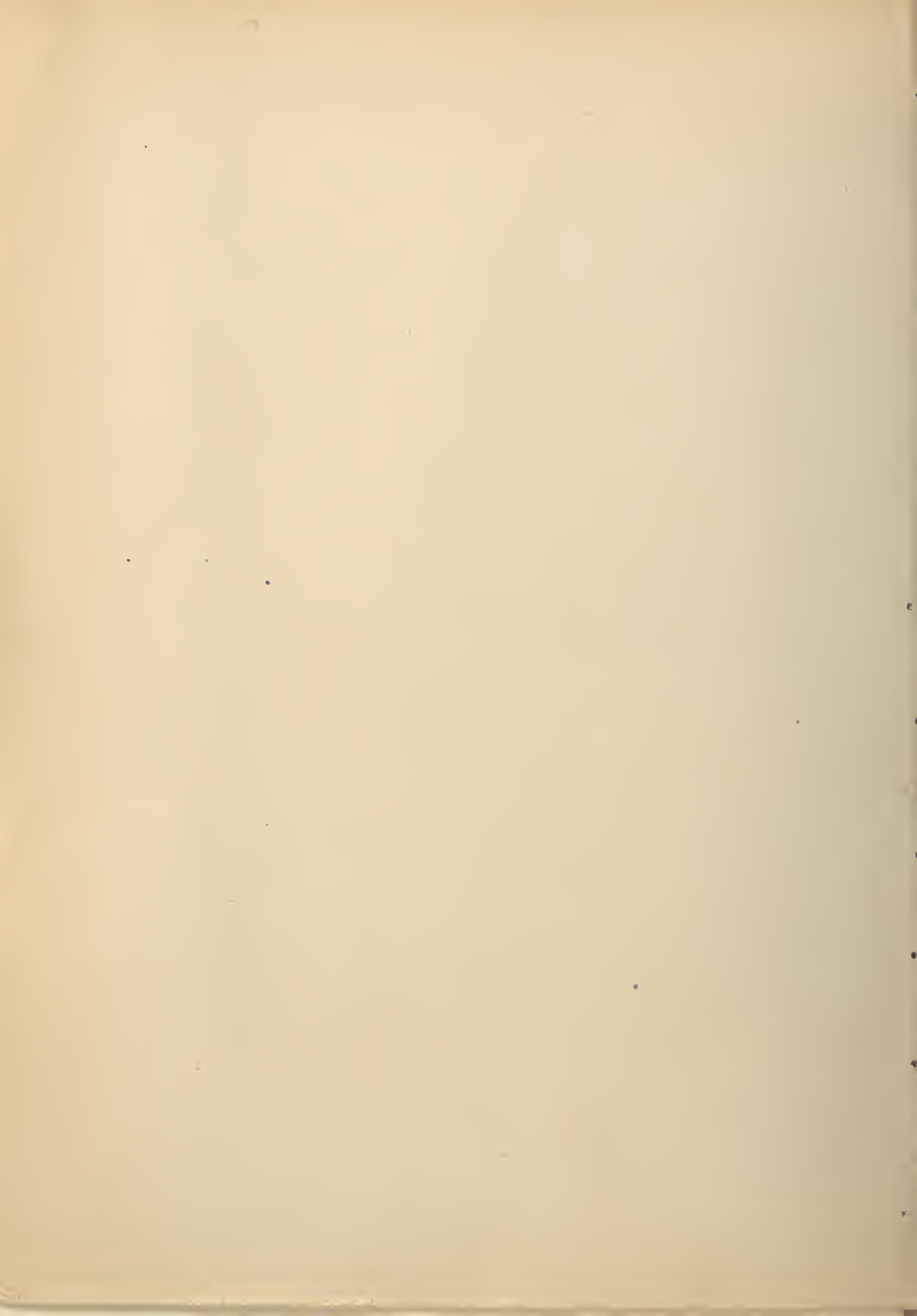
ment and the dressing is not so much needed then. It is in the intervals between the periods of actual collection and study that the oozing of gastric juice causes the cutaneous erosion. In sewing the experimental accessory stomach to the abdominal integument, the gastric juice at times penetrates along the silk sutures into the depths of the skin. All these stitches must therefore be sealed by an alkaline collodion reapplied daily, and no experimental work undertaken until healing is complete. The manner of feeding the animal during this period is described in Pawlow's original publication.<sup>1</sup>

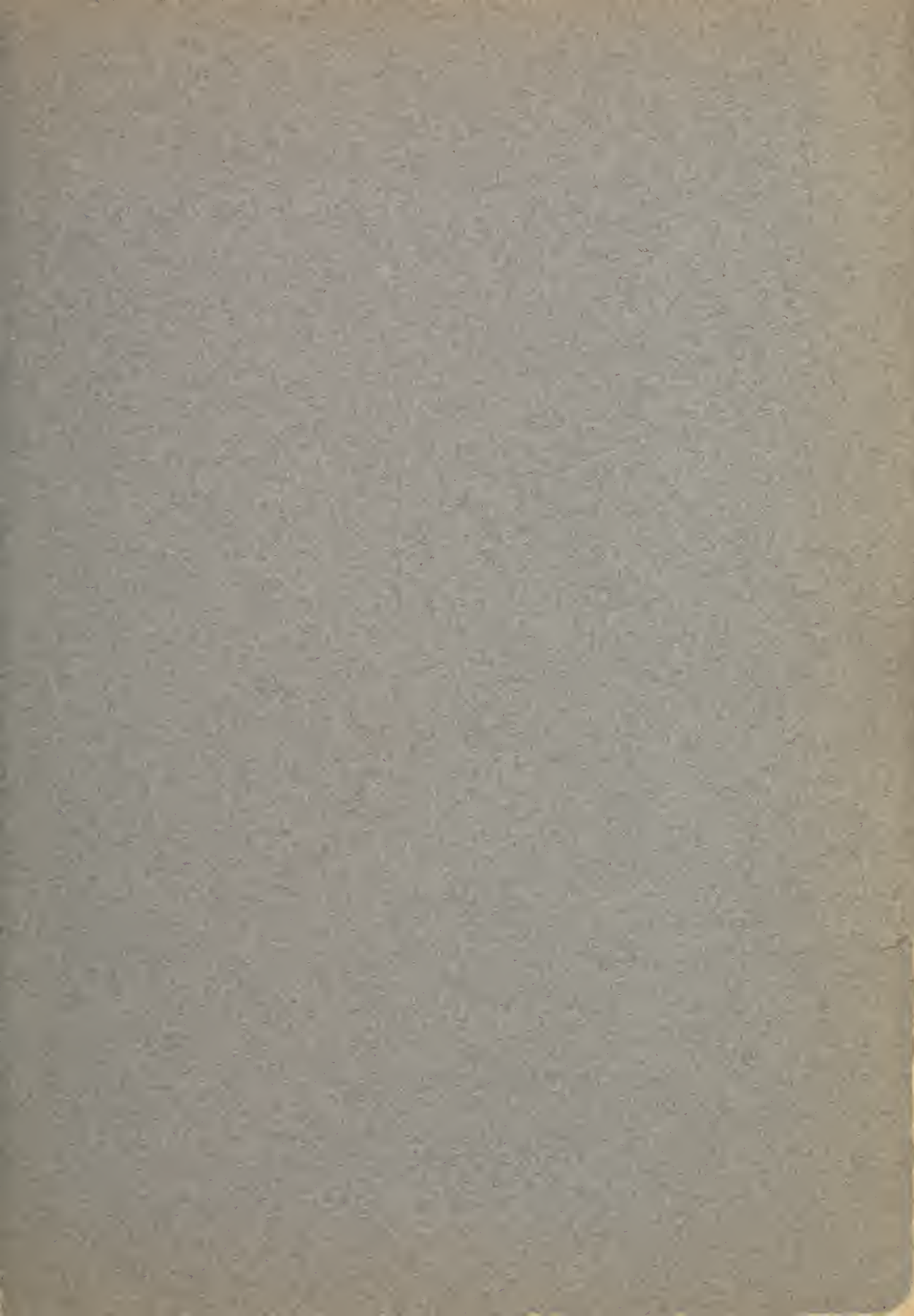
<sup>1</sup> *Loc. cit.*













THE UNIVERSITY PRESS, CAMBRIDGE, U. S. A.

THE RENAISSANCE  
OF THE UNIVERSITY  
OF MARYLAND

An Address delivered before the  
Alumni of the University,  
January 22, 1907

BY

JOHN C. HEMMETER, M. D., PH. D.,  
LL. D., Prof. of Physiology, Etc.,  
University of Maryland.

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FROM  
THE HOSPITAL BULLETIN  
BALTIMORE  
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ADDRESS BY JOHN C. HEMMETER, M. D., PH. D.,  
LL. D., PROFESSOR OF PHYSIOLOGY, ETC.,  
UNIVERSITY OF MARYLAND, ON OCCA-  
SION OF THE MASS-MEETING OF  
THE ALUMNI OF ALL DEPART-  
MENTS ON JANUARY 22D,  
1907.

"This day, January 22d, is a day of exceptional historic interest in medicine. On this day in 1720 Lancisi, a physician to the Pope and renowned for meritorious work in anatomy and pathology of the heart, died. He was the teacher of Morgagni, the actual founder of pathologic anatomy as an independent science 1682-1771.) On this day, 1851, Carl Franz Naegele, a Professor of Obstetrics in Heidelberg, an author of an excellent text-book on obstetrics, died. On this day, 1901, the great American surgeon, Lewis Albert Sayre, professor and one of the founders of Bellevue Hospital Medical College, died, at the age of 81 years. He was the inventor of a plaster of Paris corset for scoliosis, and contributed largely to medical literature of his day. On this day, in 1902, Professor Hugo Wilhelm Von Ziemssen, the celebrated German clinician, Professor of the University of Munich, died. He was the editor

of Ziemssen's Encyclopedia of Medicine. On the 22d of January, 1561, Lord Francis Bacon, the celebrated English philosopher and statesman, was born, author of the renowned work entitled, "Novum Organon." He was the originator of the inductive method of investigation, and brought about a reform of philosophy as well as of natural sciences, which caused also a great uprising in the objective investigations in all natural sciences, especially in physiology, and prepared the way for Harvey. On this day, John Frederick Blumenbach, Professor in Göttingen, died. He was the founder of the science of anthropology.

"To Lord Bacon is attributed the saying, 'A little knowledge is a dangerous thing; drink deep or not at all of the pierian spring.'

"This adage is diagonally opposed to the wisdom of Heraclitus, who in his sixteenth aphorism πολυμαθίη γουον ἔχεν οὐ διδάσκει, meaning 'much learning does not teach one to have understanding.

"But if we were to seek a well adapted sentiment to serve as a guiding line for the teaching of our University, we could not select a better one than the well known Kantian expression which Boas makes use of on the title page of his excellent work on the diseases of the intestines, namely, 'Nec Infra Nec Ultra Scire'—'not to know too little and not to know too much.'

"I was to speak to you this evening on the 'Foreshadowings of Our Centennial,' and in my mind's eye I can see the gathering of a greater

host of Alumni to celebrate the second centennial a hundred years hence. I can see the president of a world-renowned University of Maryland step out at the head of an academic procession, from a magnificent marble building, fronted with great white columns, and he will confront the cheering throng of the University's sons on a wide and beautiful green campus, adorned with classical statuary and monuments to the by-gone great teachers of the institution. And he shall refer to the hundred years which expire in May next as the 'Lombard Street epoch,' when all the buildings and institutions of the University were confined to that street, where now, he will continue to say, 'no trace of the former buildings is left; they have all been replaced by factories and stores, and on that street there was a hall belonging to a German musical society in which over 400 of the Alumni of the University of Maryland gathered on the 22d day of January, 1907, just one hundred years ago. At that time our University had really only two faculties—the Faculties of Law and the Faculties of Medicine—for the departments of pharmacy and dentistry were parts of the Faculty of Physics. Our University had then just effected its union with the ancient St. John's College, of Annapolis, whose beginnings really date back to King William's College, the old Colonial school on State House Hill, at Annapolis, which, in 1696, was the first free public school in America. In 1784, this became St. John's College.

“ ‘Now on that evening of January 22d, 1907,



this St. John's College was again united with the University of Maryland in Baltimore, the two becoming one institution; and so,' he will continue to say, 'we are in 2007, not celebrating simply the two hundredth anniversary, but if we take into account the glorious history of St. John's College and our former union with it, we are in reality celebrating our three hundredth anniversary.

" 'But the first real and earnest efforts to make a genuine university date from the final reunion of St. John's and the University of Maryland in January, 1907.' So much of prophecy.

" 'Fellow Alumni, here assembled this evening, keep your eyes fixed on this prophetic vision and do all in your power to realize this dream. From the school of medicine should develop in the next few years, a faculty of natural philosophy, bestowing the degree of Master of Arts and Doctor of Philosophy for combination studies in the natural sciences, in general biology, physiology, botany, physics, chemistry, psychology. From the Faculty of Law should develop a department of political economics. From the academic department, St. John's College, should develop a school of philosophy, ethics, logic, philology, mathematics and so on.

" 'The problem of the feasibility of having a Faculty of Theology should be taken up. There is a great deal to be learned by discussion on this subject. I can divine that we will reach the result that such a faculty, properly constituted, might be of advantage to the University of Mary-

land, especially as there is no faculty of divinity associated with any of the great universities of the East embracing all academic departments. Most of the universities that are denominational so far have not attained to complete departments in medicine and the natural sciences.

"According to Socrates, a great many of our difficulties in life as well as in the fate and management of institutions, are due to errors of conception. Some of the difficulties of the University of Maryland in the past have been due to the fact and error in conception that the managing faculties did not understand what was meant by the term 'University of Maryland.' Similarly as Louis XIV, when asked a definition of the State, said, 'L'Etat C'est Moi.' So the faculties of the University of Maryland were apt to think, if they did not say it, 'The University, that's ourselves;' and a great many times, I am sorry to say, they acted on that basis; and this is one of the reasons, perhaps the principal reason, why the University of Maryland is no farther advanced in endowment at the present day. If the faculties had not always worked 'Pour Moi,' but had worked on the broad basis, always looking for the foundation of an endowment, grappling and cementing their Alumni to the heart of the University with hoops of steel, there would have been more to show in the way of endowment at the present day. But there has been a splendid awakening of altruism in the present faculty, and the foundation of a solid endowment is highly probable as well as the organization of an inde-

pendent board of trustees. This Centennial is our great opportunity to increase our endowment, an opportunity which we should not fail to make use of.

"Master of human destinies am I;  
Fame, love and fortune on my footsteps wait;  
Cities and fields I walk; I penetrate  
Deserts and seas remote, and passing by  
Hovel and mart and palace, soon or late  
I knock unbidden once at every gate.  
If sleeping, wake, if feasting, rise before  
I turn away; it is the hour of fate  
And those who follow me reach every state  
Mortals desire, and conquer every foe  
Save death; while those who doubt or hesitate  
See me in vain, and uselessly implore;  
I answer not, and I return no more."

—*Ingalls.*

"Perhaps the most important question affecting the future, not only of science in the limited sense, but of learning of all kinds in this country, is that of the proper relation of faculties of the universities to the trustees. That the question has come into prominence at the present time is due to the fact that, since in business the tendency is towards greater concentration of power in a few hands, so, if we regard education as a business, the control of all educational questions should be in the hands of a few trustees. In the universities, however, there is the purely financial question of the management of the funds, and the question of education considered from the intellectual side; and the two questions are not only essentially different in their nature, but

also the training necessary for a business man is not the same as that necessary for one who is to be an educator and a scholar. To the trustee belongs the management of the finances, and it is preposterous to entrust purely business matters to a numerous body like the teaching faculty, even were they not unfitted for such work by their lack of training. To the faculty belong the practical work of education and to the advancement of learning by research. The difficulty at the present time is that when it comes to questions of general educational policy to be pursued there is an increasing tendency on the part of the trustees to assume that it is their business, and not that of the faculty. Practically the board which controls the expenditure of money can, if it wishes, shape the policy without regard to the opinion of others. Whether it is better for education and learning that they should do so is another matter. Probably a large portion of the educated public is of the opinion that the faculty is better qualified than the trustees to decide educational questions, both theoretical and practical, and they would certainly agree in thinking that no educational policy should be adopted without the concurrence of the faculty."

"In answer to the assertion that the trustees cannot manage the finances any better than the present faculties, it can be argued:

"I.—That the present management of the University of Maryland is considered unsatisfactory by all our alumni (almost unanimously) and even by some of the faculty itself. Every emeritus pro-



fessor, as soon as he withdraws from the active faculty advocates trustees. The work of teaching in the didactic, laboratory and clinical courses, as well as the responsibility of management in certain work of the hospital is more than sufficient for the teachers. They should be spared the administrative and financial management.

"II.—There may be considered three spheres of action or duties, for a regent in the Faculty of Medicine:

"1—Teaching.

"2—Finance.

"3—Administration.

"By administrative work I mean the duties in attending to the grounds and buildings and contracting for new work and repairs. The employment of officers, clerks, janitors, typewriters, getting up the catalogue and lecture schedule, etc., etc.

"III.—The didactic and clinical discipline is defective because the teachers are overworked in some departments and the medical faculty, for instance, has to consume so much of its time at its regular meetings by financial and administrative work, that the didactic discipline cannot be considered with that earnestness and zeal it requires. The entire medical discipline needs reformation. There should be a logical graded course of medical discipline. There must be selective courses offered to medical students. 'Concentration, sequence and election are the fruitful principals in the best modern medical education.' (W. T. Por-

ter. Preface to his laboratory text-book of physiology.)

'In 1898 the Committee of Medical Education, appointed by the Harvard Faculty of Medicine, reported in favor of the 'concentration' system urged in the committee by Dr. W. T. Porter in common with Professor W. T. Councilman, an alumnus of the University of Maryland. By this method, the first half-year in the Medical School is devoted to anatomy and histology, the second half-year to physiology and biological chemistry, the third half-year to pathology and bacteriology, and the fourth, fifth and sixth half-years to practical medicine and surgery. Work under the new system began in the collegiate year 1899-1900. In 1904, largely through the influence of Professor Bowditch, the seventh and eighth half-years were made elective, each student choosing for himself the studies best suited to his needs.

"Concentration provides that the student shall not serve two masters, but shall study at one time only one principal subject, such as physiology or pathology, disciplines that do not yield readily to a divided mind. Sequence provides that a foundation shall be laid before the superstructure is attempted. Students now have an acquaintance with anatomy before they begin the study of physiology. Election, somewhat tardily intrusts to university men rarely less than twenty-five years of age a voice in the decision of their nearest affairs. The application of these principles to medical teaching has undoubtedly resulted in large savings of time and energy.

"The economy of force secured by concentration and sequence has been highly valuable, though not indispensable, in the new teaching of physiology introduced by Prof. W. T. Porter in February, 1900. The traditional teaching of physiology consists of lectures illustrated by occasional demonstrations and, in some instances, by experiments performed by the students themselves. The new method is fundamentally opposite. It consists of experiments and observations by the student himself. The didactic instruction, comprising lectures, written tests, recitations, conferences, and the writing and discussing of these, *follows* the student's experiments and considers them in relation to the work of other observers. In the old method, the stress is upon the didactic teaching. In the new there is no less didactic teaching, but stress is upon observation. The old method insensibly teaches men to rest upon authority, but now directs them to nature.

"IV.—By continuing in the function of administration of the various faculties they place themselves in a disadvantageous position before the public benefactors and legislators because they have to defend themselves against the allegation that they are managing the financial affairs of the University to their personal interest.

"V.—On February 5, 1907, Mr. Rockefeller increased the resources of the General Education Board in New York by thirty-two million dollars. The interest of about thirty million

dollars is distributed to universities of this country annually from the funds granted by Carnegie and Rockefeller. Participation in these benefits has been denied us, the University of Maryland, on the ground that it is simply a professional school managed by the faculties, not by trustees, and that it is not a real university. The solidity of this assertion is lost by our affiliation with St. John's College. At a recent meeting, the regents of the University have appointed the following committee for the purpose of submitting a plan for the acquisition of an endowment, as well as for a general systematization of all efforts in that direction that have hitherto been made by different committees, associations, regents, trustees and individuals. The University has a Board of Trustees, incorporated by act of the legislature of the state, as *Trustees of the Endowment Fund of the University of Maryland*. The functions of this board are almost exclusively administrative, but Professor Eugene F. Cordell, the secretary, must be credited with having made the most sustained efforts at increasing its funds. The new committee, appointed by the regents, for the organization of endowments consists of the following gentlemen: Representing the Department of Medicine, Prof. J. C. Hemmeter, chairman; Department of Law, Judge Henry Stockbridge; Department of Pharmacy, Prof. Charles Caspari; Department of Dentistry, Prof. Heatewole; Academic Department, St. John's College, Prof. Thomas Fell; University Hospital, Mr. H. Busick.



#### REMOVAL OF THE UNIVERSITY TO A NEW SITE.

"I would also urge the removal of the professional schools of the University of Maryland, together with the hospitals to some new location in the northwestern section of the city, where there is a more healthy, physical and moral environment, and for this purpose I would urge on the members of the medical and dental faculty, especially the younger members, the organization of a stock company, for the purpose of purchasing land in one of the northwestern sections which are not yet improved by buildings and the erection of modern medical and surgical wards, lecture halls, laboratories and a library and administrative building. This should be considered before any further funds are spent in the construction of new buildings at Greene and Lombard streets.

The present region is being encroached upon by factories more and more; the atmosphere is thick with smoke, the noise is intolerable to the many suffering individuals in the hospital, two important car lines cross immediately through the heart of the present site of the University and add to the general turmoil, dust, restlessness and confusion. It will still be needed in part as an emergency hospital should the University ever move. There is also an increasing demoralization of this neighborhood which is a very heavy factor in determining our desire for a removal, when we reflect the danger to the psychic health of our one thousand students. A very heavy responsibility rests on the regents concerning this

latter question. They cannot escape dealing with it by any make-shift or evasive expediency. The erection of a students' dormitory on the north-west corner of Greene and Lombard streets will to a large extent prevent this demoralization.

"The idea once conceived and verified, that great and noble ends are to be achieved, by which the condition of the whole university shall be permanently bettered, by bringing into exercise a sufficient quantity of sober thoughts, and by a proper adaptation of means, is of itself sufficient to set us earnestly on reflecting what ends are truly great and noble, either in themselves or as conducive to others of a still loftier character; because we are not now as heretofore, hopeless of attaining them. It is not now equally harmless and insignificant whether we are right or wrong, since we are no longer supinely and helplessly carried down the stream of events, but feel ourselves capable of buffeting at least with its waves and perhaps of riding triumphantly over them; for why should we despair that reason that has enabled us to subdue all nature to our purposes, should (if permitted and assisted by the providence of God) achieve a far more difficult conquest and ultimately find some means of enabling the collective wisdom of our faculties to bear down those obstacles which individual short-sightedness, selfishness and passion oppose to all improvements, and by which the highest hopes are continually blighted, and the fairest prospects marred. So that from this Renaissance of the University of Maryland, there shall develop a University such

as there can be no doubt whatever what was in the minds of the organizers who formulated the plan and charter of the University one hundred years ago; namely, a *University for the People, of the People, and by the People* of Maryland.

"May this truth spread abroad with its all-absorbing power, cementing the links of our various faculties, uniting the interests of the various schools, until our university shall rise to a standard of perfection, destined by Divine Providence."







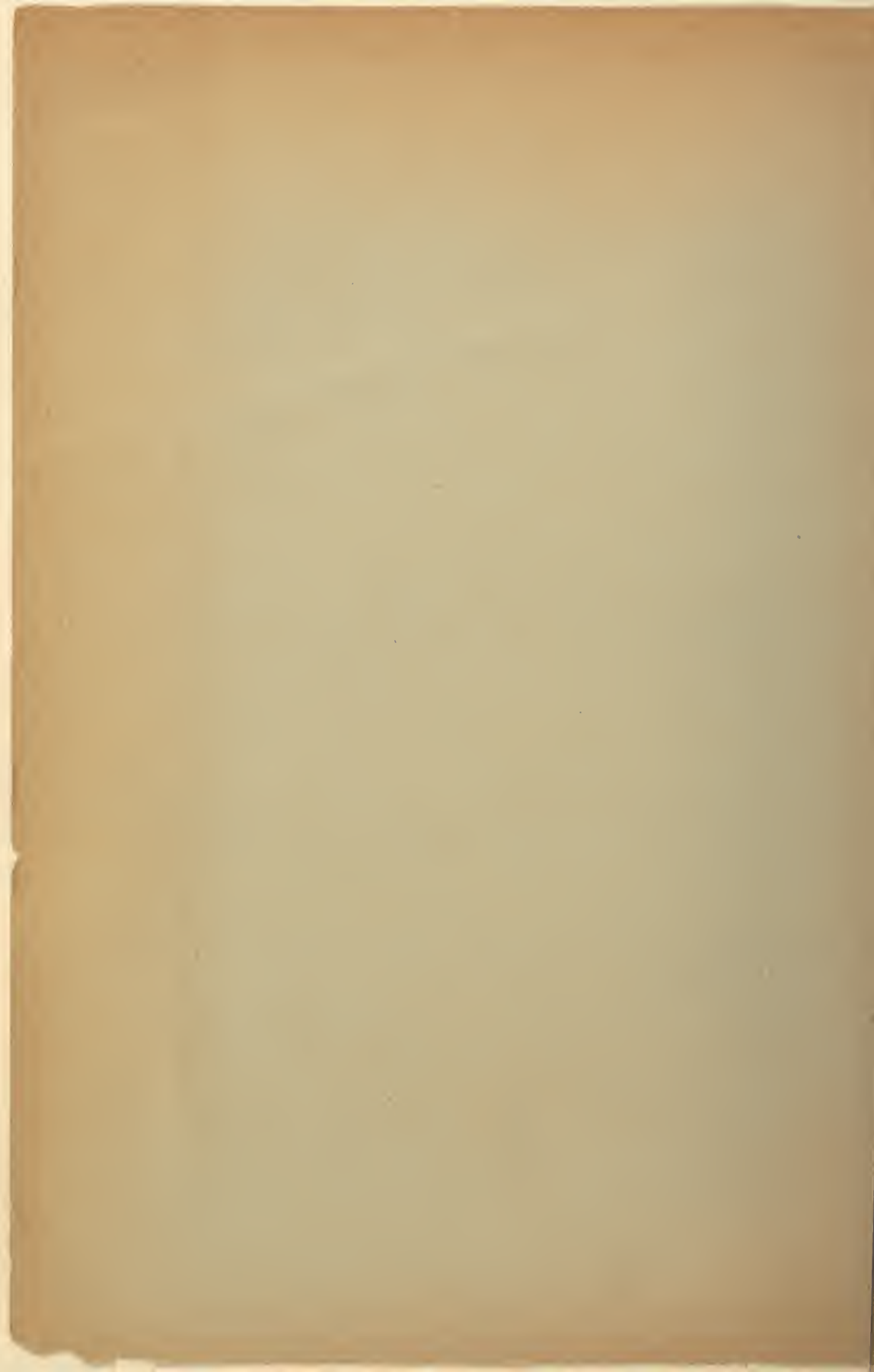
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RUDOLF VIRCHOWS LEIS-  
TUNGEN AUF DEM GEBIETE  
DER WISSENSCHAFTLICHEN  
ANTHROPOLOGIE ❀ ❀ ❀

VON

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Extrait du JANUS,  
Archives internationales pour l'Histoire de la Médecine et la Géographie Médicale.

XII<sup>e</sup> ANNÉE, LIVRAISON X, 1907.



# RUDOLF VIRCHOWS LEISTUNGEN AUF DEM GEBIETE DER WISSENSCHAFTLICHEN ANTHROPOLOGIE.

*Rede gehalten bei der Ueberreichung einer Büste Virchows an die  
Medizinisch-Chirurgische Fakultät von Maryland zu Baltimore, Jan. 1. 1907.*

VON JOHN C. HEMMETER, M.D., PHIL. D. LL.D.,  
*Professor of Physiology and Clinical Professor of Medicine,  
University of Maryland.*

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## EINLEITUNG.

Da es mit guter Begründung voraussetzen war, dass diese Versammlung hervorragender Kliniker mit den medizinischen-, speziell, pathologisch anatomischen Leistungen Virchows hinreichend bekannt war, habe ich es auf Ersuchen unseres hochgeehrten Vorsitzenden unternommen, eine Seite der Thätigkeit Virchows zu beleuchten, die dem Kliniker und praktischen Arzt selten nahe gebracht wird; es wird mir daher zur angenehmen Pflicht, die anthropologischen Errungenschaften dieses Geistesheroen zu besprechen. Es wird zu entschuldigen sein, wenn ich hierbei unterlasse, eine ausführliche Biographie und Bibliographie beizufügen. Man findet die meisten Referate in den Berichten der Anthropologischen Gesellschaften, die im Text dieser Rede genannt sind. Auch in der Geschichte der Patholog. Anatomie von H. Chiari in Neuburger u. Pagels Handbuch der Geschichte der Medizin, Bd. III, 536—541. Auch einer Rede von Prof. Boas, welcher den Lehrstuhl der Anthropologie in der Harvard Universität zu Boston inne hat, muss ich gedenken; dieser Rede habe ich viele interessanten Gesichtspunkte entliehen (publ. in "*Science*", New-York 1902). Es macht dieser Aufsatz keinen Anspruch auf wissenschaftliche Vollständigkeit, sondern soll bei dieser Feier nur dazu dienen, eines der wichtigsten Talente Virchows vor Augen zu führen und dadurch in dem Verständniss des Praktikers die collosale Vielseitigkeit des Forschers ergänzen.

## RUDOLF VIRCHOW'S ANTHROPOLOGISCHES WIRKEN.

In Rudolf Virchow hat die Wissenschaft einen ihrer leitenden Geister, Deutschland einen seiner grössten Söhne und die Welt einen ihrer bedeutendsten Männer verloren. Sechzig Jahre lang hat Virchow mit eminentem Können und unermüdlichem Fleiss sich der Menschheit gewidmet.



Die medizinischen sowohl als die anatomischen und anthropologischen Wissenschaften deuten auf ihn als einen ihrer gediegenten Gelehrten. Jahrelang übte er einen gewaltigen Einfluss auf das politische Leben Deutschlands aus, immer das Prinzip der persönlichen Freiheit aufrecht erhaltend.

Die Anfänge seiner anthropologischen Arbeiten fallen beinahe mit den allerersten Anfängen der modernen physikalischen Anthropologie in Deutschland zusammen. Unter denen, welche diese Wissenschaft ins Leben riefen, hat keiner mehr zur Bildung, Führung und Förderung derselben getan als Rudolf Virchow.

Seine Aufmerksamkeit wurde zur Zeit dadurch auf die Anthropologie hingelenkt, der er den Stempel seiner Persönlichkeit aufdrücken sollte, dass er sich mit Untersuchungen über die Ursachen des Cretinismus beschäftigte und über Mittel und Wege nachsann, um die Vorbedingungen der Entwicklung des Schädels festzustellen. Die Ähnlichkeit pathologischer Formen des Schädels und die Formen verschiedener Rassen haben ihn jedenfalls zu Untersuchungen über die Variationen der menschlichen Körperformen hingeführt.

Die Grenzen seines anthropologischen Wirkens erweiterten sich bald sehr schnell und der Trieb zu weiter greifenden Arbeiten den er, besonders in der physikalischen Anthropologie und in der prähistorischen Archäologie, veranlasste, war so gross, dass man mit Recht sagen darf, die Entwicklung dieser beiden Teile der Wissenschaft in Deutschland bewegen sich um Virchow als Centrum.

Zur Zeit als Virchow seine Arbeiten aufnahm war die Anthropologie noch in ihrem Anfangsstadium. Während des 18. Jahrhunderts hatten von Soemmering und Blumenbach in Deutschland und Camper [Peter Camper, Prof. d. Anat. in Amsterdam u. Groningen, zuletzt im Haag empfahl die Rassen und deren Intelligenz nach dem Gesichtswinkel zu beurtheilen (+ 1789)] in Holland ihre Aufmerksamkeit dem Studium anatomischer Eigenarten der menschlichen Rassen gewidmet, doch die neue Anthropologie erwachte nicht vor der zweiten Hälfte des vergangenen Jahrhunderts. Der starke Trieb, den die Evolutionslehre allen Wissenschaften verlieh, verbunden mit dem Interesse, welches die Urgeschichte der europäischen Völker beanspruchte und den sich stets erweiternden Kenntnissen fremder Rassen waren die Hauptfactoren, welche die moderne Anthropologie ins Leben riefen.

Virchow hat durch seine aussergewöhnliche Begabung für Organisation das Bereich der Anthropologie nach allen Richtungen gefördert. Er nahm eine führende Stellung ein in der Bildung der „*Deutschen Anthropologischen Gesellschaft*“, der „*Berliner Gesellschaft für Anthropologie, Ethnologie*

und Urgeschichte" und in der Gründung des monumentalen „*Archiv für Anthropologie*“, welches einen hohen Rang in der anthropologischen Literatur einnimmt. Die beiden Gesellschaften wurden bald die Centren anthropologischen Wirkens in Deutschland. Die Deutsche Anthropologische Gesellschaft widmete ihre Bemühungen dem Studium physischer Charakteristiken und der Urgeschichte der Deutschen. Unter Virchow's Leitung unternahm diese Gesellschaft eine Sammlung von Statistiken über die Distribution der Haut-, Augen- und Haar-Farben in Deutschland und Beobachtungen wurden in allen öffentlichen Schulen des Reiches angestellt. Das Ergebniss dieser ausgedehnten Untersuchung, welche eine cartographische Darstellung der Distribution von Typen in Deutschland und eine Abhandlung über ihre wahrscheinliche Geschichte umfasste, wurde von Virchow herausgegeben.

Die Berliner Gesellschaft für Anthropologie, Ethnologie und Urgeschichte wurde bald eine Stätte, wo sich eine Menge anthropologischen Materials von allen Weltteilen ansammelte und wo wichtige wissenschaftliche Fragen durch anerkannte Autoritäten verhandelt wurden. Durch seine intimen Beziehungen zu deutschen Reisenden, trug die Gesellschaft wesentlich zur Entwicklung des *Berliner Ethnologischen Museums* bei, dessen Gründung und Bedeutung Adolf Bastian zu verdanken ist. Durch Virchow's Einfluss kam die Gesellschaft in den Besitz einer grossen und wertvollen Sammlung von menschlichen Schädeln und Skeletten. Unter den Gegenständen, die behandelt wurden, nahm die europäische Archäologie immer eine hervorragende Stellung ein. Virchow nahm grossen Anteil an dieser Arbeit, welche wesentlich zur Entwicklung der prähistorischen Sammlungen in Berlin beigetragen hat.

Als Director des Pathologischen Instituts und Museums der Berliner Universität, hatte Virchow weitere Gelegenheit das Studium der Anatomie der Rassen zu fördern. Er sammelte viel wertvolles anthropologisches Material in diesem Institut. Sein Studium der prähistorischen Archäologie brachte ihn in Berührung mit Forschern über Volksitten und Gebräuche und dadurch wurde er Mitbegründer des *Museums für Volkstrachten*.

Hieraus lässt sich schon erschen, dass Virchow die erste Stelle in der Organisation anthropologischen Wirkens in Deutschland einnahm. Es nimmt deshalb nicht Wunder, dass seine Ansichten einen weit reichenden Einfluss ausgeübt haben bis zu einem solchen Grade sogar, dass man die Eigenart der deutschen physikalischen Anthropologie und der deutschen prähistorischen Archäologie überhaupt nicht verstehen kann, ohne mit seinem Wirken vertraut zu sein.

Von grösster Wichtigkeit ist sein Verhalten den Theorien gegenüber, welche sich mit der Descendenz-Lehre beschäftigen. Seine Ansichten

hierüber wurden durch seine gründlichen Forschungen über die Functionen der Zelle im Tier-Organismus bestimmt. Seine Ansichten fasste er in den Worten zusammen, dass jede Zelle von einer anderen abstammt. Ganz einerlei wie die Zellen in ihrer Form von einander abweichen, jede neue Form bedingt eine ältere. Zellen mögen im Verlauf ihres Daseins ihre Form, je nach ihrem Alter oder anderen Einflüssen, denen sie ausgesetzt sind, verändern. Solche Veränderungen finden sowohl in dem gesunden wie in dem kranken Organismus statt und oft wird es unmöglich, zwischen normalen, oder physiologischen und anormalen, oder pathologischen Veränderungen zu unterscheiden. Virchow selbst drückte sich dahin aus, dass es überhaupt nicht möglich sei, zwischen physiologischen und pathologischen Processen, welche unter erschwerenden Umständen sich vollziehen, eine Grenzlinie zu bestimmen. Die Zelle, welche ihre Form während ihres Lebens wechselt, mag schon deshalb als veränderlich oder variable betrachtet werden; mit Virchow's eigenen Worten, sie besitzt *Mutabilität*. Nach seinem Dafürhalten läuft die ganze Frage der Abstammung auf das Problem der Beziehung zwischen der Veränderlichkeit des Organismus und der Veränderlichkeit der Zellen hinaus. Das vergleichende Studium der Formen des Organismus und der Organe mag den Ausgangspunkt der Forschungen über Veränderlichkeit bilden, aber das Studium des ganzen Organismus oder Organs muss sich auf das Studium der Veränderungen der Zellen selbst stützen, da die physiologischen Veränderungen des ganzen Körpers von den correlativen physiologischen Veränderungen der einzelnen Zellen abhängen. Ohne Verständniss für die Processe, die in den sich verändernden Zellen stattfinden, ist es unmöglich festzustellen, ob eine Abweichung von der normalen Form durch *secundäre* Ursachen, welche *schon ausgebildete* Organe angreifen, hervorgerufen wurde, oder ob dieselbe von *primären* Veränderungen, welche *vor der ersten Gestaltung* des Organs stattfanden, veranlasst wurde.

Hieraus ergeben sich also zwei Fragen.

I. Erstens, ob secundäre Veränderungen erblich werden können. Überzeugende Beweise hat man hierfür nicht.

II. Zweitens, ob primäre Veränderungen überhaupt stattfinden, und ob, in dem Falle, dieselben erblich sind.

Von diesen Ansichten ausgehend verlangt Virchow, dass Forschungen über die Entstehung der Arten sich auf Forschungen über die Mutabilität der Zellen und Zellgruppen stützen und deshalb weigert er sich, über die Entstehung der Arten Betrachtungen anzustellen bevor man durch Forschungen über Zellgewebe eine feste Grundlage gelegt hat. Manchmal will es scheinen, als ob Virchow den wissenschaftlichen Wert der Evolutions-Lehre in Zweifel zöge. Doch lässt sich eine solche Vermuthung nicht



beweisen. Er betont einfach immer wieder den methodisch-logischen Standpunkt, dass das Verständniss der Formen des Körpers auf Verständniss der Formen wechselseitiger Beziehungen und Functionen der Zellen sich stützen muss, und dass deshalb die Frage der Veränderlichkeit erst durch Forschungen auf die angegebene Weise beigelegt werden muss.

Überdies stützt sich seine Stellungnahme auf das allgemein wissenschaftliche Princip, dass es gefahrvoll ist, Tatsachen, die man bloss teilweise versteht, den Wert von allgemeinen Theorien beizumessen, und dass der wahre Fortschritt einer Wissenschaft davon abhängt, dass man sich in jeder wissenschaftlichen Erörterung stets völlig klar darüber ist, wann man es mit Hypothesen zu tun hat und wann mit Tatsachen, die durch genaue Beobachtung ermittelt worden sind. Diesem Princip ist Virchow mit grosser Festigkeit treu geblieben bis zu dem Masse sogar, dass Mancher über-eifrige Schüler und Gelehrte seine ruhige und vorsichtige Kritik als ein Hinderniss des wahren Fortschritts betrachtet hat. Er ist deshalb manchen bitteren Angriffen ausgesetzt gewesen, bis endlich die fortgeschrittene Forschung bewies, dass der Meister doch recht hatte, als er sich weigerte, Schlussfolgerungen aus mangelhaften Beweisen zu ziehen. Es gibt wenige Gelehrte, welche eine solche ruhige und verständige Zuneigung für die Wissenschaft besitzen, dass sie gerade deshalb immer im Stande sind, eine scharfe Grenzlinie zwischen einer anziehenden Theorie und einer durch lange und schwere Arbeit ermittelten, Beobachtung zu ziehen.

Es gibt zwei anthropologische Probleme, welche besondere Wichtigkeit in ihrer Beziehung zu der Evolutions-Lehre besitzen; die eine betrifft das Alter des menschlichen Geschlechtes und die andere bezieht sich auf die Auslegung anatomischer Charakteristiken der niederen Rassen. Kenntnisse, welche sich auf die anatomische Gestaltung des Urmenschen beziehen, sind in der Anzahl sehr beschränkt. Jahrelang beschäftigte man sich hauptsächlich mit der Auslegung des Neanderthal Schädels, welcher einige merkwürdige Eigentümlichkeiten aufweist; ganz besonders eine platte, flache Bildung des Schädels und bedeutende Erhebungen über den Augenbrauen. Virchow bewies, dass der Schädel viele pathologische Veränderungen durchgemacht hatte und er nahm den Standpunkt ein, dass es unvorsichtig wäre, eine neue Rasse, welche gewissermassen als Vorläufer des menschlichen Geschlechtes zu betrachten wäre, von diesem einzigen Exemplar herzuleiten. Er zog es vor, diesen Schädel als eine individuelle Variation zu betrachten bis weitere Funde bestätigendes Material liefern würden. Virchow war auch genau so vorsichtig in der Auslegung von theromorphischen Veränderungen des menschlichen Körpers. Er behauptete, dass solche Formen nicht notwendigerweise auf Atavismus hindeuteten, dass sie aber von eigenartigen physiologischen Processen herkommen können



und dass, ohne besondere Untersuchung ihrer Entstehung, sie nicht als Beweis einer niederen Organisation der Rassen, unter denen man sie wiederfindet, zu betrachten seien. Es sind keine Beweise vorhanden dass solche Formen mit einer niederen Kultur des Volkes, unter welchen man sie vorfindet, zusammenhängen. Man findet sie zum Beispiel unter den Malayen und unter den alten Peruvianern, welche beide Völker sich doch gewiss in der Kultur hoch entwickelt haben.

Es ist nicht möglich sich an dieser Stelle, innerhalb des Umfangs dieser Skizze, mit Virchow's vielen Untersuchungen, die Anatomie der menschlichen Rassen betreffend, zu beschäftigen. Viele enthalten Erörterungen von allgemeinen Principien. Ganz besonders bedeutend sind seine Forschungen über die physikalische Anthropologie der Deutschen und seine Beschreibungen amerikanischer Schädel.

Seine Untersuchungen über die anatomischen Eigentümlichkeiten der Deutschen führten ihn natürlicherweise dem Studium der prähistorischen Archäologie zu, der er viel Zeit und Arbeits-Kraft widmete. Seit längerer Zeit hielt man Formen des Körpers für nationale Charakteristiken. Formen des Schädels wurden als teutonisch und slavisch beschrieben; man sprach auch von turanischen und vielen anderen Arten von Schädeln. Niemand hat mehr als Virchow dazu beigetragen, die Unhaltbarkeit dieser Annahmen zu beweisen.

Fragen, die Geschichte der slavischen Niederlassungen in Ost-Deutschland betreffend, sind viel von deutschen Archäologen behandelt worden und doch ist manches darüber im Unklaren. Obgleich Begräbniss-Ceremonien, prähistorische Gegenstände, Orts-Namen, Auslegung von Dörfern und Häusern stark auf frühere slavische Niederlassungen hindeuten, so kann man andererseits keinen Schluss in Bezug auf die Nationalität der Ureinwohner aus dem gegenwärtigen anatomischen Bau der Bevölkerung und der alten Skelette ziehen, da weder die Deutschen noch die Slaven einen gleichförmigen oder charakteristischen anatomischen Typus aufweisen. Virchow hat immer behauptet, dass die Grenzen der menschlichen Typen sich nicht mit den Grenzlinien der Kulturen und Sprachen decken. Angehörige eines gewissen Typus mögen verschiedene Sprachen und verschiedenartige Kulturen haben; und andererseits, wie das in Deutschland der Fall ist, treffen verschiedene Typen in einer Nation zusammen.

Diese Erscheinungen hängen intim mit den complizirten Wanderungen der europäischen Rassen zusammen; mit den Eroberungs-Zügen der teutonischen Völker nach Süd-Europäischen Ländern und die Entwicklung der Nord-Europäischen Kultur durch den Einfluss der Ost-Mediterranischen Kulturen. Die allmähliche Einführung von Metallen und das Verschwinden der Kultur des Steinalters ist ein Phänomen von grösster Wichtigkeit

zur Aufklärung der wechselseitigen Beziehungen der verschiedenen europäischen Urvölker. Der Kultur-Wechsel, durch die Einführung der Bronze angegeben, deutet darauf hin, dass die neue Kultur in dem fernen Osten sich aufschwang. Aus dieser Ursache unternahm Virchow seine ausgedehnten prähistorischen Studien in Klein-Asien und im Kaukasus. Seine Studien auf dem Gebiete der prähistorischen Archäologie, welche dem Anschein nach so weit entfernt von seiner ersten anatomischen Arbeit sind, stehen in Wirklichkeit in sehr intimen Beziehungen zu seinen Forschungen, die Urgeschichte der europäischen Rassen betreffend. Anatomische Thatsachen allein können diese komplizierten Probleme nicht lösen und Virchow's weit greifende Tätigkeit auf dem Gebiete der prähistorischen Archäologie ist ein weiterer Beweis seiner gründlichen und umfassenden Methode, welche alle Mittel benutzt, um wissenschaftliche Probleme zu lösen.

Die physikalische Anthropologie und die prähistorische Archäologie in Deutschland sind zum grössten Teil das geworden, was sie sind, durch Virchow's Einfluss und Wirken. Seine Arbeits-Weise, seine Ansichten, seine Ideen waren und sind jetzt noch die bedeutendsten, seine Grösse als Gelehrter verdankt er einer seltenen Vereinigung von kritischem Urteilsvermögen, von grösster Einsicht, Tüchtigkeit und Gründlichkeit verbunden mit einem encyclopädischen Wissen und einer Fähigkeit, die unwesentlichen Beziehungen der Phänomene als solche richtig zu erkennen.

Sein kritisches Urteilsvermögen war so eigenartig erstarkt, dass er in einer Ansprache im Sommer 1900 sogar das Wünschenswerte seines starken Einflusses auf die öffentliche Meinung in Frage zog.

Mit grosser Bewunderung und innigem Gefühle der Dankbarkeit betrachten wir sein Lebenswerk, welches das Wesen einer neuen Wissenschaft bestimmt hat.

In seinem klassischen Werk, „*Griechische Denker*“ sagt Theodor Gomperz (Bd. III, S. 27):

„Man kann zwei Grundtypen des Weltweisen unterscheiden. In dem einen überwiegt das Verlangen nach Wissenfülle, die Unersättlichkeit im Aufnehmen immer neuen und mannigfaltigen Erkenntnisstoffes; in dem anderen das Streben nach innerer Widerspruchslosigkeit, nach unbedingter Folgerichtigkeit des Denkens. Es ist das selbstverständlich nur ein Unterschied des Grades; keines der beiden Elemente kann dort vollständig gefehlt haben, wo hervorragende philosophische Leistungen erzielt sind. Aber die Verschiedenheit ist darum eine nicht minder wirkliche. Ein Stein um Stein zu einem einheitlichen Denkgebäude fügender Descartes oder Spinoza und ein in Einzeluntersuchungen jeglicher Art unermüdlich sich tummelnder Leibniz oder Aristoteles stellen zwei weit voneinander abweichende Abarten einer gemeinsamen Gattung dar. Der von ruheloser Detailarbeit in Anspruch

genommene Encyklopädist mag noch so eifrig nach *strenger Geschlossenheit* seines Gedankenbaues trachten: sein Bemühen wird niemals von ebenso vollständigem Erfolge gekrönt sein, wie jenes eines gleichwertigen, aber nicht von gleich starkem Drang nach „*Polymathie*“ beseelten und dadurch zerstreuten Intellectes. Der Klärungstrieb aber wird in diesem eine eigenartige Richtung nehmen. Er wird dem Bedürfnis nach Anordnung und Einteilung eines ungeheuren Wissensstoffes dienen. Der Encyklopädist wird auf stoffbeherrschende *Kunstgriffe* sinnen, wie Leibnizens Begriffssprache einer war, oder er wird zum Klassifikator par excellence erwachsen.“

Zu welchen von diesen Grundtypen gehört nun Virchow? Je gründlicher unsere Vertrautheit mit der geistigen Entwicklung dieses intellektuellen Titanen, — je erschöpfender unsere Einsicht in seine Leistungen — je überzeugender unser Verständniss seiner gewaltigen Förderungen menschlichen Denkens und Könnens; je aufrichtiger müssen wir unser Unvermögen bekennen, diesen Mann in irgend eine der Gomperz'schen Grundtypen einzureihen.

Denn, — wir haben vor uns einen Denker, der die Charakteristiken beider Typen in sich vereint: — a) Verlangen nach Wissenfülle, Unerstättlichkeit im Aufnehmen immer neuen und mannigfaltigen Erkenntnisstoffes und b) Streben nach innerer Widerspruchslosigkeit und unbedingter Folgerichtigkeit des Denkens.

Bei der heutigen gewaltigen Entwicklung der Künste und Wissenschaften wird es nicht möglich sein, dass die menschliche Rasse einen Denker hervorbringe, der befähigt wäre, wie Aristoteles in alle Zweige der menschlichen Erkenntnis seiner Zeit einzudringen. Es wäre dies der Entwicklung der Rasse kaum förderlich. Denn schon bei Heraclitus findet man Aphorismen, die das Unerwünschte dieses Gedankens genügend klar ausdrücken. In seinem 16. Aphorism sagt dieser Griechische Denker *πολυμαθία νόον, ἔχειν ὅτι διδάσκει* (zu): „Viel des Wissens bringt oder gibt nicht die Einsicht (oder das Verständniss).“ Der heutige Stand menschlicher geistiger Errungenschaften verlangt — als Bedingung seines Fortschritts — eine möglichste Concentration mentaler Energie. Das Beherrschen eines gewaltigen Erkenntnisstoffes, die *πολυμαθία*, führt jedoch eine Zerstreutheit des Intellectes herbei. (Wie *Theodor Gomperz* das sehr richtig ausdrückt. *Griechische Denker*, III. Bd. S. 27.) Und ein solcher Zustand des Intellectes kann unmöglich zur Entdeckung neuer Wahrheiten führen, kaum noch zu objectiver Detailarbeit befähigen.

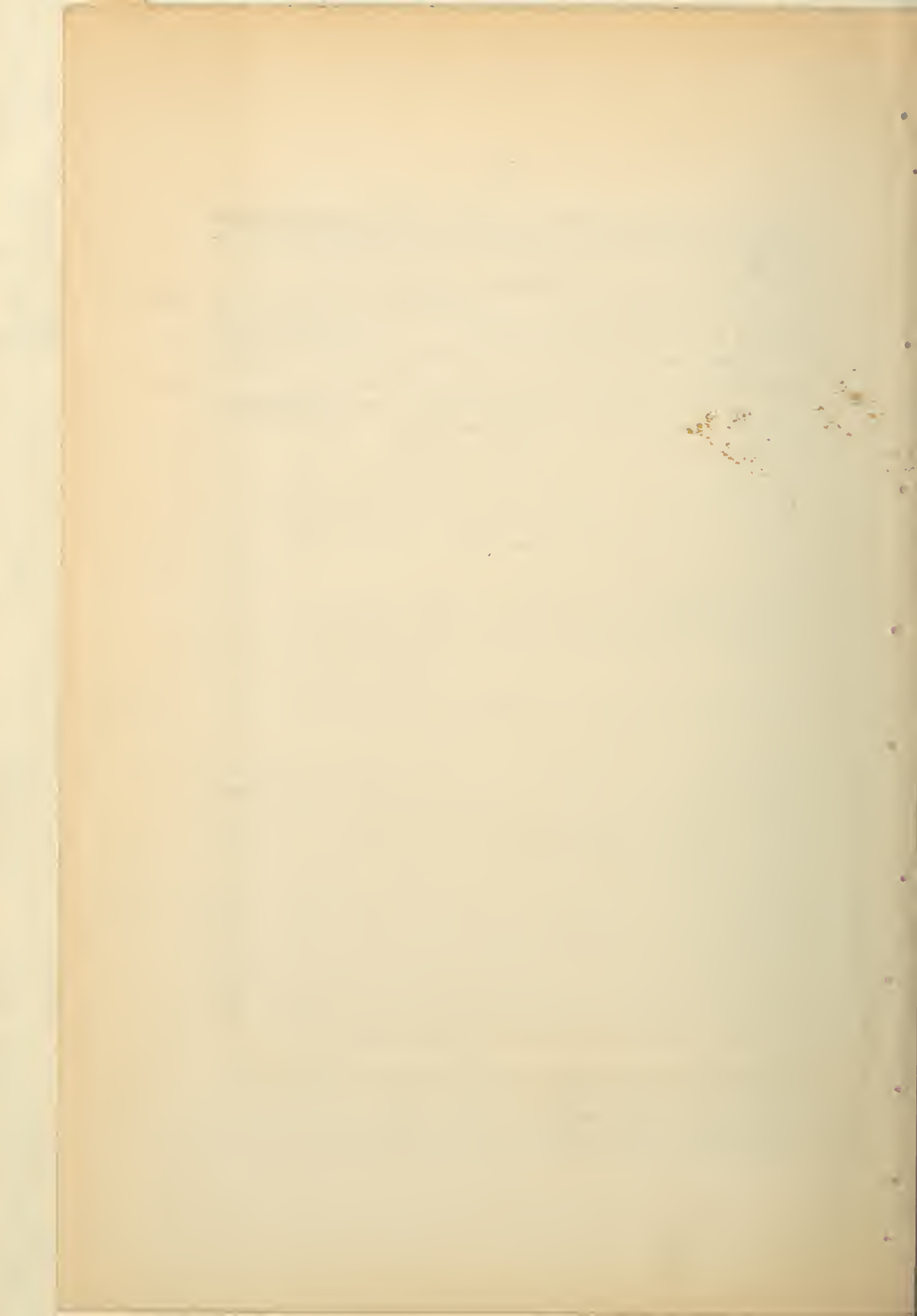
Das Erstaunliche in dem Gedankenbau unseres modernen Asklepiaden und Naturphilosophen ist die seltene Verbindung von Fülle des Wissens, Gedankenreichtum, ausgezeichnetem klassifikatorischem Talent und objectiver Beobachtung. Dabei einer Leichtigkeit in der Systematisierung,

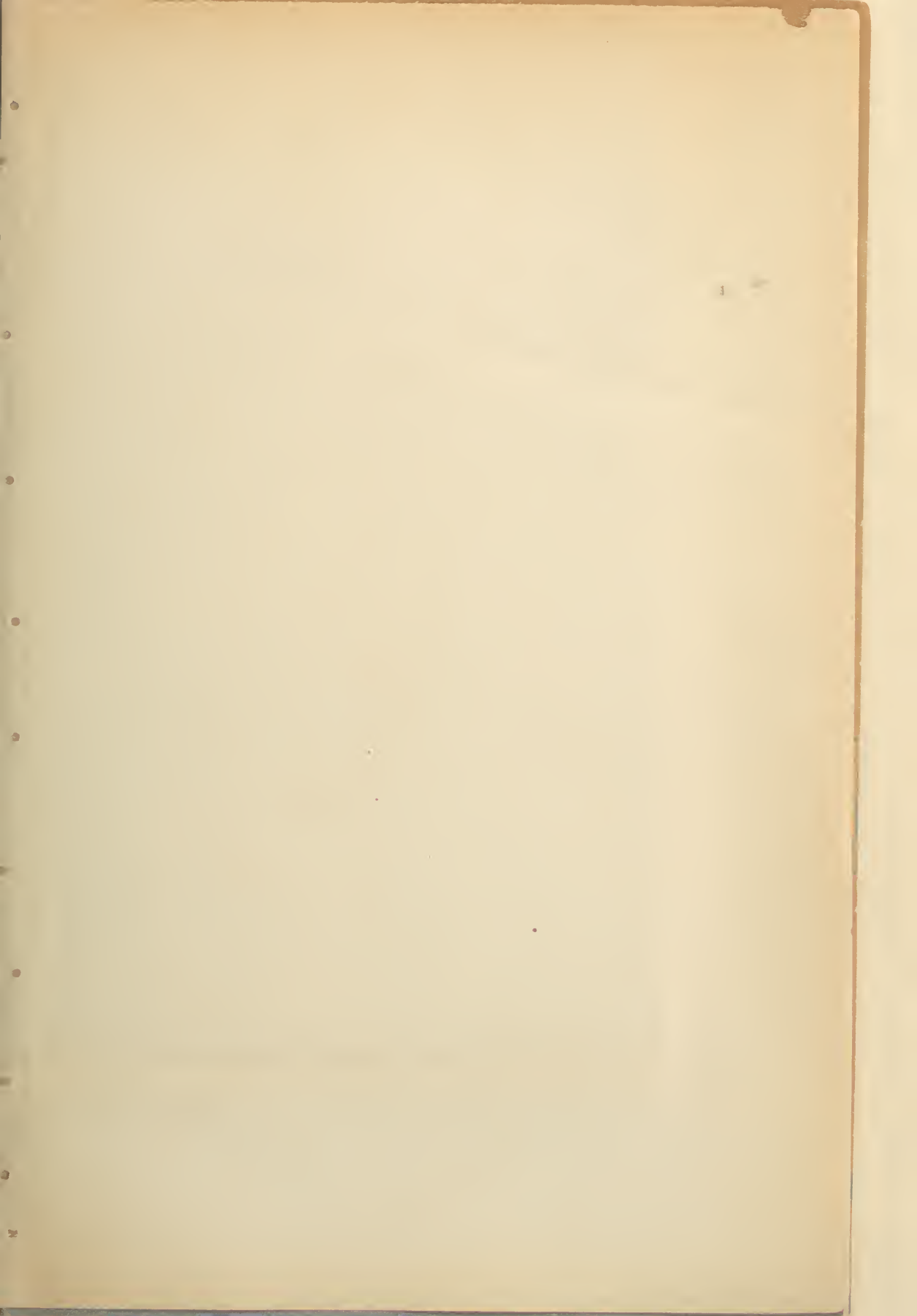
im Ordnen und in der Gliederung des Wissensstoffes, welche den antiken „*Syllogismus*“ des Aristoteles an Objektivität und Genauigkeit bei Weitem übertrifft.

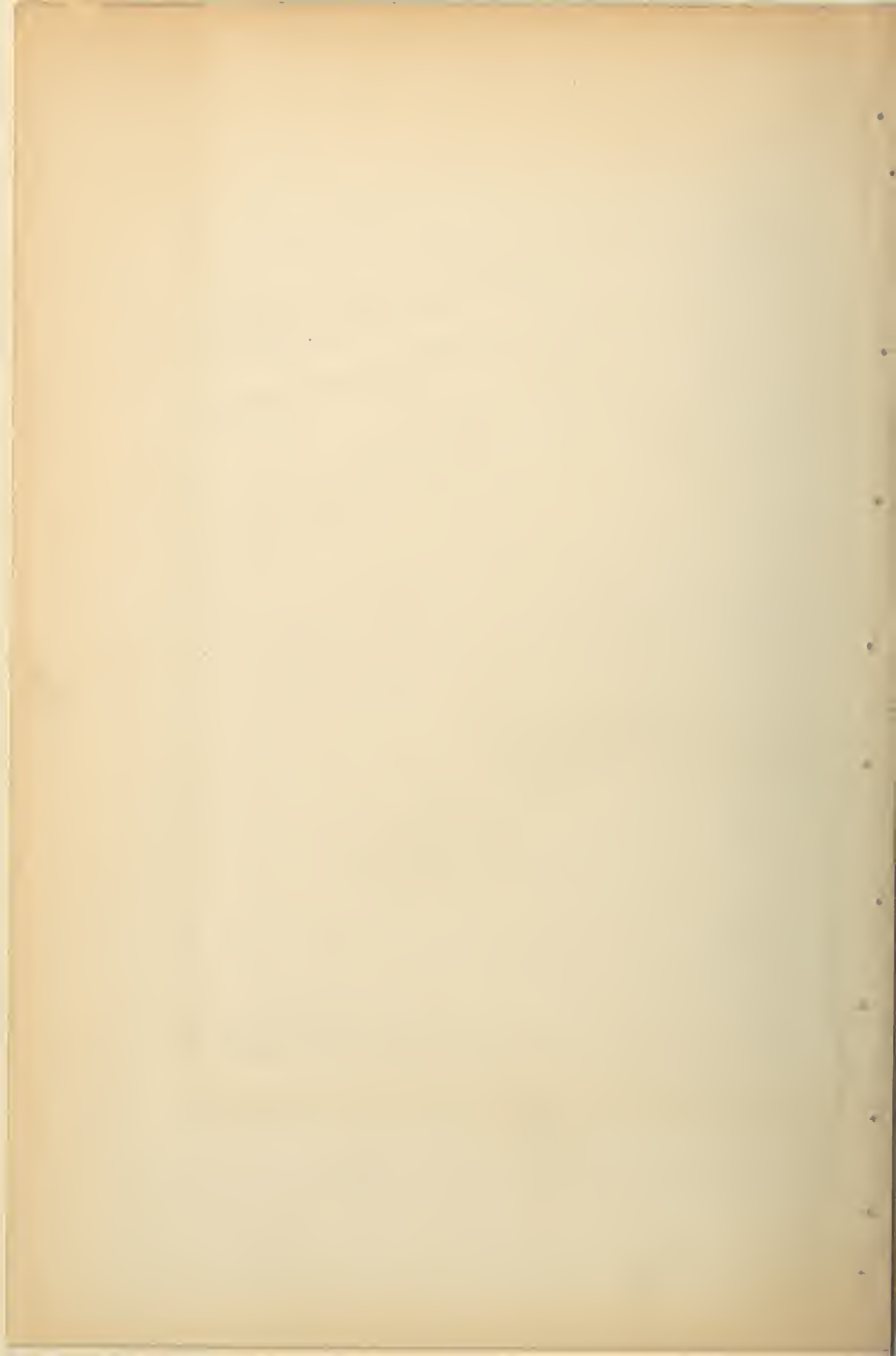
In Anbetracht eines so gewaltigen menschlichen Daseins, wie es das Leben Virchow's war, muss das Vertrauen unserer Rasse in sich selbst erstärken, und obschon für das Individuum die kurze Spanne des Lebens nur geringen Fortschritt zum Ziel des Vollkommenen bietet, so beweist doch ein solches Leben und Wirken, dass menschliche Wissenschaft und Kunst, was die Fähigkeit zu objectiver Entwicklung und Vervollkommenung anbetrifft, unbegrenzt sind. Ὁ μὲν βίος βραχύς ἡ δὲ τέχνη μακρά (Hippocrates).

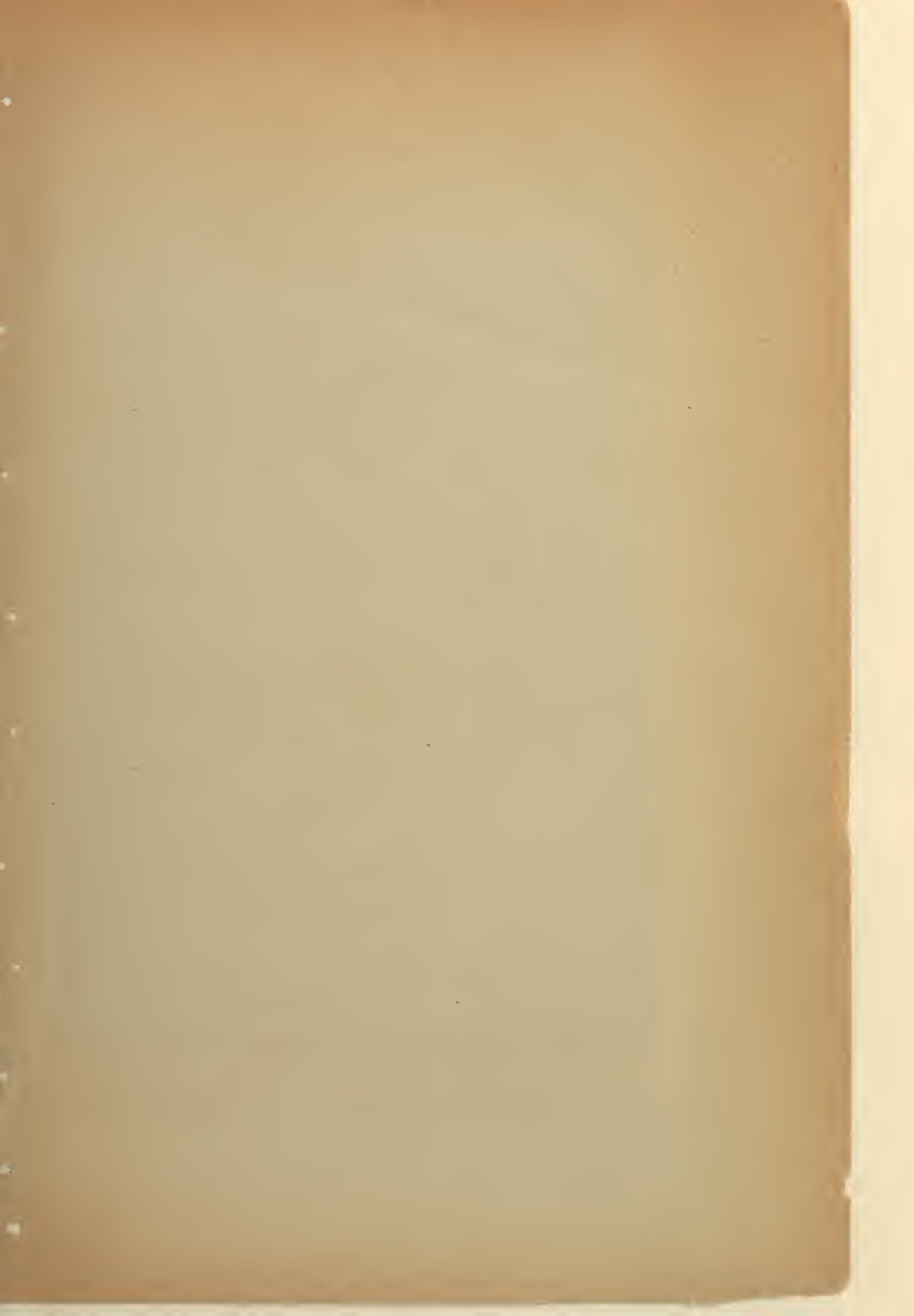
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Compliments of Author.

# EXPERIMENTAL BASIS OF THE DIETETIC AND MEDICINAL TREATMENT OF HYPER- ACIDITY AND GASTRITIS.

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Presented to the Section on Materia Medica, Pharmacy and Therapeutics, at the Forty-eighth Annual Meeting of the American Medical Association, held at Philadelphia, Pa., June 1-4, 1897.

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REPRINTED FROM  
THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION,  
OCTOBER 9, 1897.

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CHICAGO:  
AMERICAN MEDICAL ASSOCIATION PRESS.  
1897.



## EXPERIMENTAL BASIS OF THE DIETETIC AND MEDICINAL TREATMENT OF HYPERACIDITY AND GASTRITIS.

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BY JOHN C. HEMMETER, M.B., M.D., PH.D.

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Boas, who first used the finding of fragments of mucosa in the vomited matter and gastric wash water for diagnostic purposes, attributed great importance to this way of finding out the real state of the mucosa. He held that, in certain conditions of suppressed secretion, the differential diagnosis between a possible neurosis and a genuine gastritis with a glandular atrophy was only possible by examination of such pieces of mucosa. Rosenheim, Boas and Julius Friedenwald, *Med. News*, June 22, 1895, emphasize the value of qualitative and quantitative testing of rennet zymogen to differentiate between chronic gastritis with glandular atrophy and carcinoma on the one hand, and nervous dyspepsia and secondary gastritis on the other. However, Ewald and also Einhorn have asserted that absolute deficiency of rennet zymogen is not pathognostic for atrophy, therefore it would indeed seem as if a certain diagnosis could only be made by a small piece of mucosa.

Is there any clue which can be derived from these pieces regarding the state of the mucosa in the secretory disorders? This I will try to answer in the following. Hayem, to whom we are indebted for the best histologic investigations of the gastric mucosa, emphasizes that the individual elements of the mucosa, gland ducts, superficial epithelium and interstitial tissue can become diseased in a variety of ways; the



various portions of the stomach fundus, pylorus and cardia may exhibit different affections; and finally the mucosa may at different parts show different phases of disease. He distinguishes a parenchymatous and an interstitial gastritis. First the parenchymatous:

1. *Gastrite parenchymateuse hyperpeptique chloro-organique*.—Under this he has two subclasses: *a, d'emblée*—dyspepsia coming on at once, in the first stage of digestion; *b, tardive*—coming on in later stages, in one and one-half to two hours. Under this hyperpeptic parenchymatous gastritis Hayem means, clinically, a hyperpepsia with hyperacidity, and anatomically, degeneration of the principal central or chief cells with proliferation of the parietal border or oxyntic cells.

2. *Gastrite parenchymateuse muqueuse*—"gastritis mucipara," by which he means a mucous degeneration, a process taking place principally in the vestibules to the gland ducts (which are lined with columnar epithelium), and corresponds to the Schleim Katarrh of most German writers. This is associated with hyperpepsia and subacidity.

3. *Gastrite parenchymateuse atrophique*, which signifies anatomically the total atrophy of the glands without interstitial processes, and clinically, anacidity or achylia. The interstitial forms he separates into two classes: those in which the round cell infiltration, and those in which the sclerosis, *i. e.*, connective tissue proliferation, predominates. These processes are described as occurring purely as such, or mixed with forms of parenchymatous gastritis, and as leading to sub- or anacidity. In order to bring my results in critical consideration with those of Einhorn, I have adopted his classification of the anatomic conditions found in these fragments. There is, however, one objection that can be urged against it, and that is the apparent fact that he has based his system on conditions of the gland tubes and interglandular tissues exclusively, and mentions the state of the cells only once in six types described. I will therefore supple-

ment his categories by adding the state and condition of the vestibular or alveolar columnar cells (Vorraum Zellen), and the condition and numeric relations of the chief, central or ferment cells (Hauptzellen) and the parietal, border or oxyntic cells (Belegzellen).

1. Normal. Gland ducts and interglandular tissues exist in normal proportions. Columnar epithelium of the surface and that of vestibule normal, with scarce cells showing at their free ends slight mucoid metamorphosis. The average number of parietal or oxyntic cells in six ducts which were sectioned very nearly down the center was twenty-two to forty.

2. Connective tissue excess. Proliferation of connective tissue around the glands, glands and epithelial cells as in normal condition.

3. Proliferation of glands. Under this class I have in nineteen cases been impressed with the probability that there must be three types of this condition:

Type *a*.—In this subtype there is a proliferation of gland tubules. Under the same field of microscope there will be more than under normal conditions, since they are much closer to each other, but the number of central and oxyntic cells are from eighteen to forty-two, or the same as under the normal condition.

Type *b*.—Increase of oxyntic or parietal cells with normal number of gland ducts. Here there seems to be no proliferation of the gland ducts, the connective tissue and the ducts bear the same relation as in class 1, but the anilin staining, oxyntic cells may be so increased that they lie in juxtaposition, giving the whole duct the appearance of a peptic duct of the dog; the number may reach seventy in one duct. The oxyntic cells are increased in size; the nuclei stain very dark.

Type *c*.—Increase of the number of ducts in which the number of oxyntic cells appear normal in size and number, and in the same fragment or section portions of mucosa in which the ducts are not augmented, but the oxyntic cells are increased in number and size; this third is then, it would seem, a combination of

types *a* and *b*. When there are many oxyntic cells above the normal, the entire gland duct assumes a tortuous or elongated shape. It seldom extends down into the mucosa in the same plane, therefore it is very rare that a section will strike down the middle of a duct. Generally the counts in six ducts struck fairly along the central canaliculus are taken as an average.

4. Incipient atrophy. To the same field under the micrometer there are fewer glands than normally present. They appear shrunken and smaller, and at the same time the spaces between the glands are larger than normal, owing to an increased connective tissue formation; the latter is thickly invaded as a rule, with small round cell infiltration.

5. Atrophy. In complete atrophy there are only remnants of glands left, a few degenerated cells lying in empty circular spaces where glands had previously existed; there is also a diffuse round-celled infiltration.

6. Vacuolization. Round or ovoid vacuoles exist within the glands in large numbers, being the result of mucoid degeneration of some of the glandular cells; this is generally associated with connective tissue proliferation. Vacuoles are present in the gland cells normally and can be seen in the drawings of Kupfer and Stöhr. I have also seen them in both longitudinal and cross sections of the gland tubules, but rarely more than two to three to the entire duct. It is conceivable that they may be produced by the process of hardening and imbedding. Some of the fragments obtained from stomachs may show characteristics of two types.

#### DEDUCTIONS FROM THIRTY-SIX CASES.

In eight *healthy* persons the mucosa fragments were normal in six; proliferation and autodigestion marked in one, which also showed beginning small round cell infiltration between the ducts; connective tissue increase in one. In the first of these cases the examination showed proliferation in one fragment and a normal condition in a second one found in the same wash water.

In eighteen cases of *hyperacidity*, the fragments of gastric mucosa were found apparently normal in four; atrophy of gland tubules and connective tissue increase so that there were fewer glands, but in these few there were contained a larger number of oxyntic cells than normal, in two cases; proliferation of gland ducts with apparently normal oxyntic cells in six cases; proliferation of oxyntic cells, generally without marked increase in the gland tubules, in six cases.

In twelve cases of *anacidity* or *subacidity* the fragment was apparently normal in two cases; proliferation of glands with marked small round cell infiltration was found once. Atrophy in some form was found in the fragments from the nine remaining cases.

In establishing the classification of *euchlorhydria* and *hyperchlorhydria* we could not be guided exclusively by the amount of free HCl found after the double test meal used at the Maryland General Hospital and described in the author's book (Hemmeter, "Diseases of the Stomach," p. 111. P. Blakiston Son & Co., Philadelphia, 1897). Thus, a young, vigorous farmer, aged 25, who had never had any disease, showed on repeated examination an amount of free HCl equal to 60 degrees, with a total acidity of 80 degrees. Ordinarily, judging simply from the analysis, such a case would be diagnosed as *hyperacidity*. However, these cases can be diagnosed justly and accurately when considered together with concomitant signs and symptoms only. Although this case had the large amount of free HCl, there was no starch indigestion, no erythrodextrin, no pyrosis; there were no symptoms referable to the stomach at all, the man was in perfect health.

Another case, a neurasthenic female, had intense suffering from *hyperacidity* and occasional *gastroxynsis*, and the amount of free HCl was never over 30 degrees. This case showed *hypermotility*. The stomach as a rule was empty twenty-five minutes after an Ewald test meal; with my intragastric rubber bag in connection with the kymograph, she showed very



frequent and sudden gastric peristalsis of unusual tonicity.

#### SUMMARY.

Eight *healthy* persons: Perfectly normal in six; *a.* glandular proliferations; *b.* normal in 1; connective tissue increase in 1.

*Hyperacidity* in eighteen cases: Normal in four; atrophy in two; proliferation of glands in six; proliferation or hypertrophy of oxyntic cells in six.

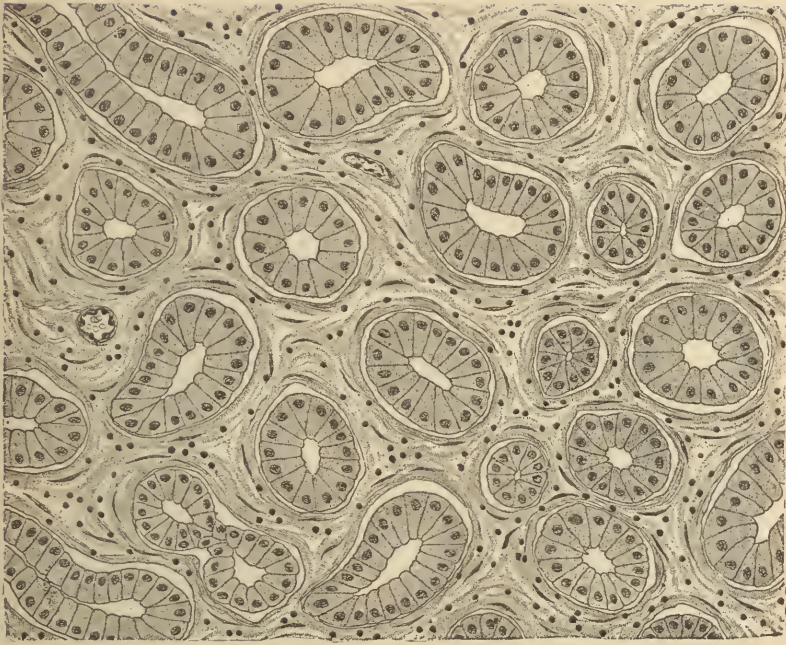
*Anacidity or subacidity*: Normal in two; proliferation of glands in one; atrophy in nine.

Proliferation, therefore, according to this table is present in two-thirds of these cases of hyperacidity, and atrophy in three-fourths of these cases of anacidity or subacidity. Einhorn does not give any results from examination of perfectly healthy individuals as his cases of *euchlorhydria* seem to be in patients.

Of his twelve hyperacid cases three were normal or very nearly so, six showed proliferation and three showed connective tissue proliferation. In his cases of anacidity, or rather what he calls *achylia gastrica* of which there were seven cases, there was atrophy three times, marked vacuolization once, proliferation once, and normal condition twice.

On the whole, judging from Einhorn's results, Cohnheim's, Hayem's and my own, the conclusions seem justifiable that proliferation of glandular elements is present in from one-half to two-thirds of the cases of hyperacidity, and atrophy is present in from one-half to two-thirds of the cases of anacidity.

Adolf Schmidt (*Virchow's Archiv*, Bd. cxliii, S. 478), asserts that the epithelium of the stomach is preserved better than the gland cells in inflammatory conditions of the mucosa. This he says is particularly so in chronic gastritis which forms island-like foci in stomachs otherwise not much changed. My experience and that of W. D. Booker, is not in accordance with this observation (see pathology of simple, acute and chronic gastritis in the clinical portion of Hemmeter's "Diseases of the Stomach"). Although I preserved



● Fragment of mucosa showing normal condition of glands; very slight round-celled infiltration. From Hemmeter's "Diseases of the Stomach." P. Blakiston Son & Co., Philadelphia, Pa., October, 1897.

the stomachs by injecting them with alcohol immediately after death (within twenty minutes), also with formalin and sublimate so that autodigestion was at once checked, my sections showed generally a more serious destruction of the surface epithelium than of the gland cells. At times both are so much altered that it is impossible to say which is most or least affected. It seems in chronic gastritis that new epithelium will be reformed quite rapidly where the old has been lost or destroyed.

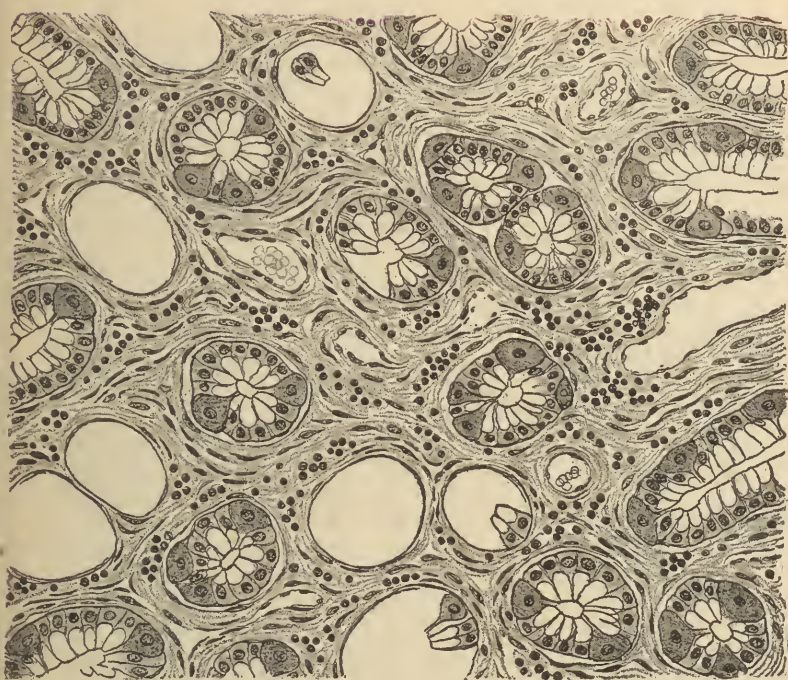
In suspected cases of malignant neoplasms fragments of the growth are occasionally found and are of importance in the diagnosis. In carcinoma of the cardia or esophagus they are most frequently found in the lower or side opening of the tube, as it must pass through or over the growth on its way into the stomach; but even in malignant growths of other parts of the stomach, patient searching in the sediment of the wash water will sometimes reward the clinician by the discovery of tumor fragments. The first wash water in the morning, about 500 c.c., should be permitted to settle twelve hours in a conical glass such as is used for the settling of urinary solid constituents, and the sediment should be examined under a low power (about 50 diam.) or the sediment may be more expediently brought down in the centrifuge.

Once I made the diagnosis of carcinoma when no tumor was evident from repeatedly finding involuntary muscle fibers when no meat had been eaten for three days after preceding lavage. It proved to be a broad, flat carcinoma of the posterior wall.

The sections were stained in a variety of ways, principally in the eosin-hematoxylin, Golgi and Bismarck brown stains. The minute communications of the oxyntic or parietal cells with the central duct are best brought out by the Golgi method.

The drawings of fragments found in the wash water of glandular proliferation with glands closely packed and connective tissue diminished, and of glandular atrophy, mucoid degeneration, vacuolization, and small





Atrophy and vacuolization of glandular elements; mucoid degeneration of chief or central cells; comparative preservation of border or oxyntic cells; from a case of gastritis acida. From Hemmeter's "Diseases of the Stomach," P. Blakiston Son & Co., Philadelphia, Pa.



cell infiltration are all explained by the text accompanying the illustrations. These drawings are taken from the author's text-book, "Diseases of the Stomach." We have seen that histologic changes approaching or actually representing pathologic states may be going on in perfectly healthy stomachs. Furthermore, the stomachs of diseased patients may on serial sections show a different pathologic state at different places of the mucosa. Therefore, it must be borne in mind that although the findings in hyperacidity and anacidity appear to be in some relation to the disease, this kind of investigation must not be relied on as representing in a given fragment the condition of the entire mucosa. It represents the state of the location from whence it sequestered, and that not being accurately known generalizations must be made with caution.

It is therefore rational to presume that there are at least two kinds of hyperchylia: One which is of neurotic origin and in which the acid elements of the mucosa are not hypertrophied or augmented, and the other in which the neurotic symptoms are absent, or at least not very marked, and in which a decided proliferation of the secreting cells of the gland ducts can be made out. It is conceivable also that in the neurotic type, although there may be no hypertrophy and increase in the number of gland cells at the beginning of the disease, the constant demand upon and stimulation to the increase of acid and ferments may, in the course of the disease, eventually bring about an oxyntic cell, hyperplasia and hypertrophy. Eninger explains the anatomic changes in the spinal cord and nerves by a disproportion of the function of activity and the replacement of nervous elements; an increased activity of an organ leads to straightening of the same and increase in its volume; inactivity leads to a weakening and atrophic state of an organ. W. Roux ("Entwicklungs-Mechanick der Organismen," 1895) uses the expression "each cell gains a living by work, and the more it works the better it is nourished and the stronger it grows." In hyperacidity the elements that



Hypertrophy and proliferation of glandular elements, from a case of persistent hyperacidity.

come more into play and do more work will increase in strength and numbers and gain supremacy. Dujardin-Baumetz and F. Sohlern (*Berlin. Klin. Wochschr.*, 1891, 20 and 21); Fleiner (Volkmann's *Klin. Vortr.*, 103) and Rummo (*Terapia clin.*, 1892, Nos. 10, 11 and 12), recommended a largely carbohydrate diet in gastric diseases accompanied by abnormal production of acid. We have satisfied ourselves personally, after a very large number of quantitative chemic analyses of the gastric contents of healthy individuals after they had taken weighed amounts of pure proteid and pure carbohydrates, that the proteid articles of diet are greater stimulants to the secretion of HCl than the carbohydrates or fats. They therefore stimulate and irritate the secretory layer to a greater formation of hydrochloric acid; this has been experimentally proven to a certain extent by v. Jacksch in children. It is also known that the great variations stated by different authors as to the amount of free HCl that is normal in their localities are explicable by the nature of the various test-meals used by them. The amount of free HCl after the complex test-meal of Riegel and Fleiner is much greater than after a simple test breakfast which contains very little proteid. It must not be overlooked that an exclusive proteid diet causes the formation of excessively large quantities of soluble peptones and albumoses, which undoubtedly have an exciting action on the nervous system and constitute a favorable basis for the development of all kinds of neuroses. Although a diet rich in meat food is perfectly logical and correct in hyperacidity, careful quantitative analyses of the urine will show that the indican, the ethereal and preformed sulphates are very much more increased under this kind of diet, and that they become reduced as soon as the amount of carbohydrates is increased. Beef, mutton, lamb, venison, fowl and various fishes, undoubtedly relieve the main complaints of hyperacidity for a time. The gastric pain and the pyrosis disappear for a time at least, because the albumin



contained in the substances combines with the excess of HCl, but in cases in which a lasting improvement is not affected by these articles of diet, and where the urotoxic coefficient, the amount of indican and aromatic sulphates become increased it is advisable to try a diet in which the proteids do not constitute the preponderance, but at least 50 per cent. of which is composed of fats and carbohydrates.

The following tables show the state of the urine in a case of hyperacidity, both under proteid and under a carbohydrate diet. The case suffered as a rule from auto-intoxication when the proteid food was in excess.

#### URINARY ANALYSIS.

*Case 19.*—April 12, 1896. W. M., male, age 35 years, hyperchylia, on proteid diet exclusively; no medicine. Free HCl=48.5 after Ewald test breakfast.

Indigo blue . . . . .	very strong
Urea . . . . .	22.712 grams
Uric acid . . . . .	0.451 grams
Ratio . . . . .	49.0
Preformed sulphates . . . . .	1.826 grams
Combined sulphates . . . . .	0.236 grams
Ratio . . . . .	7.7

The combined ethereal sulphates and the indigo are present here in great excess; headache and much flatulence.

*Case 19.*—May 12, 1896. W. M., hyperchylia, Free HCl=59. Mixed diet, containing rice, bread, oatmeal, together with small quantities of beef or soft-boiled eggs, and milk and butter. Neutralization with alkalies and aiding the gastric amylolysis with ptyalin at one meal and taka-diastase at another.

Indigo blue.. . . .	very faint
Urea . . . . .	42.641 grams
Preformed sulphates . . . . .	4.000 grams
Combined sulphates . . . . .	0.350 grams
Ratio . . . . .	11.0

Patient feeling much better, less headache, debility and flatulence. This is an example of twenty analyses, showing that even with an excess of HCl the proteid putrefaction may be considerable and that the symptoms are relieved and the urine shows less of toxins on a mixed diet with treatment by ferments and alkalies.

These are only two examples of a series of eighteen analyses.



It is undeniable that carbohydrates are found undigested six hours after they are ingested, in the wash water from the stomach. This is what one should expect, since if the excess of hydrochloric acid is not neutralized by alkalies, the ptyalin can not act and it is impossible for carbohydrates to be converted into a soluble form, the HCl at the same time producing a pyloric spasm obstructing the passage into the duodenum. Even with a diet almost exclusively of a proteid nature, the alkalies are indispensable, as this food is in itself inadequate to combine with the excess of acid. We advise our patients to take their amylaceous foods in a very finely divided state when possible. Potatoes should only be allowed in form of purée. Beets, turnips and carrots should not be allowed at all. The artificially prepared soup meals (Kufeke's, Maggi's flour, Maltoleguminose) and soups made from aleuronat, and oatmeal flour are in these cases easily digested with the aid of artificial diastase or ptyalin. It is a very important question whether the diastatic ferment of the saliva is destroyed permanently or only temporarily by the excess of hydrochloric acid and whether after its action has been inhibited by the acid it can be restored by subsequent alkalization. Boas ("Diagnostik u. Therap. d. Magenkrankh.," p. 19) has demonstrated that when saliva is exposed to the action of 0.15 per cent. HCl for one hour its action can be restored by alkalization with bicarbonate of soda. In hyperacidity the percentage of acid reached is 0.2 per thousand of HCl; in severe cases 0.4 to 0.6 per thousand HCl. We have made a large number of experiments with the effects of hydrochloric acid on saliva, both with artificial test-tube experiments as well as experiments from stomach contents of patients suffering with hyperacidity, and have found that, although Boas's results are in the main true, the action of ptyalin after it has been exposed to an acidity of 0.3 per thousand for forty minutes can not be restored to the same efficiency it showed before it was subjected to the action of the acid; that is, alkalization restores

the action only partially. The conversion of starches by this ptyalin which has been thus detrimentally influenced by HCl takes place only very feebly, in other words, the ptyalin does not recover perfectly, it has been permanently damaged. These experiments have been repeated so often by us and the results have been so constant that they could not possibly be due to accident. They justify us in the conclusion that the internal administration of alkalies in hyperacidity will not restore gastric amylolysis although the distressing symptoms of hyperchylia will be relieved by it. It is therefore necessary, if we wish to aid digestion of starchy foods and not simply relieve the distressing symptoms of hyperacidity, not to depend on restoration of the function of ptyalin by giving alkalies. The employment of artificial ptyalin or diastase is here unavoidable; ptyalin, one-half to one gram (8-15 grains) given fifteen minutes before meals together with alkalies, effectively converts the carbohydrates into dextrose. The more carbohydrate is artificially digested in this way, the less undigested starch will naturally remain in the stomach. We will naturally, therefore, give the preference to a ferment which can in the shortest time convert the greatest amount of carbohydrate into dextrose. We have made a number of experiments with ptyalin and the diastase contained in malt extract, but the most effective agent that we have worked with is a ferment known as taka-diastase. This has the property of being far less susceptible to the destructive action of hydrochloric acid than ptyalin or malt extract. The objection we have to malt extract is that we have to give it in a large bulk to get a very small quantity of diastase. The extract itself contains fermentable sugars which, in some cases of indigestion, may give rise to fermentation in the stomach. Taka-diastase is a substance obtained from a fungus known as *euotium oryzae*, which is sown on moistened sterilized wheat bran. A growth results which is found, under the microscope, to present peculiar crystals of pure diastase covering the

roots of the eurotium which have penetrated the bran. The function of these crystals is to convert the starch of the bran for the nourishment of the fungus. We have employed taka-diastase in hyperacidity and in these rare cases of deficiency of saliva, which are found in the final stages of chronic Bright's disease, and after severe diarrheas. Malt diastase and ptyalin cease acting in the stomach contents much sooner than taka-diastase with a percentage of HCl equal to 0.04 per thousand to 0.05 per thousand of HCl, taka-diastase will still transform more than 50 per cent. of starch into maltose. The following experiments will throw some light on the digestive power of taka-diastase. A starch paste was made from 5 grams of dry arrow-root starch with 500 c.c. of water. Mixtures were then made as follows:

1. 0.5 gram of taka diastase + 90 c.c. of water + 10 c.c. of starch paste.
2. 0.5 gram of ptyalin + 90 c.c. of water + 10 c.c. of starch paste.
3. 20 gram of malt diastase + 90 c.c. of water + 10 c.c. of starch paste.

These three mixtures were placed at 40 degrees C. and tested from time to time with iodine solution. In periods of time varying from five to eight minutes No. 1 had reached the achromic point, while No. 2 had not reached the achromic point until one hour had elapsed. At the end of three hours No. 3 still gave a bluish violet reaction with iodine. In the presence of 0.015 HCl the action of the ptyalin and the malt extract were arrested, whereas the action of the taka-diastase continued unhindered. We therefore give taka-diastase because of its more effective and permanent amylolytic power, because of its cheapness, and because we are enabled to permit a diet rich in carbohydrate in cases of hyperacidity. The most essential thing in the treatment of an irritable gastric mucosa is rest for a short time, two or three days in every week; no food but milk or thin oatmeal gruel. To give meat and egg with a view to combine with the excess of HCl is only symptomatic treatment.

But an amylaceous diet aims at the cause of the hyperacidity, because it is not a stimulant to HCl secretion and does not add to the irritation already present.

In recommending a carbohydrate diet in hyperacidity we are aware that it will generally not be tried until the proteid diet has failed to give permanent relief. The amylaceous diet is to a certain extent antiseptic by its tendency to keep the intestinal chyme acid by formation of lactic acid. The quantitative analysis of indican and ethereal sulphates will keep one posted on the degree of intestinal putrefaction under the two kinds of diet.

It is well known that hyperchylia often occurs in neurasthenia due to uric acid diathesis. The diet must then naturally be adapted as far as is consistent with the gastric function to the uric acid diathesis underlying the whole complication of symptoms (see *Diät bei Gicht und Harnsäure dyskrasie*, Penzoldt u. Stintzing, Vol. ii).

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## DISCUSSION.

Dr. C. B. LOWE of Philadelphia—I had the pleasure yesterday of meeting the Japanese chemist, Dr. Takamine, the discoverer of taka-diastase. The remarkable activity of this amylolytic ferment was demonstrated by his placing a few grains in a test tube containing starch paste. After adding it, either in the dry form or as a liquid, the solution began immediately, and in a moment or two the contents of the tube were liquefied and converted. The experiment was a very striking one and demonstrated the great power possessed by this agent in the digestion of starchy articles of food.

Dr. K. G. ECCLES of Brooklyn—Did I understand the lecturer to say that maltose would be absorbed from the stomach? I was under the impression that all starchy foods passed into the intestine where it was converted into dextrose by the pancreatic juice and the intestinal secretion. Perhaps Dr. Hemmeter will set me right on this point. I am not sure whether I fully understand his position in reference to the use of taka-diastase in cases of hyperacidity. It would seem to me that most of the starchy foods are not digested in the stomach, although the proteids are acted upon there.

Dr. F. E. STEWART of Detroit—In reference to the question of the absorption of maltose into the blood from the stomach,

I would say that I am under the impression that Professor Chittenden found that it was not essential that the starch be entirely converted before being absorbed. Dr. Roberts of London found that the glycogen of the liver is very much like the same products of starch digestion.

Dr. ECCLES—I would like to add that I have tried taka-diastase on myself and on patients and have found the results from it to be very good. I therefore was not criticising the treatment but merely desired information upon the physiologic and chemic basis of the method of treatment advocated by Dr. Hemmeter.

Dr. FRANK H. MURDOCK of Pittsburg, Pa.—I have been exceedingly interested in Dr. Hemmeter's paper. I think that the question of hyperacidity of the stomach is one of very great importance and one which offers the most difficulty to me in my practice. If we can have within our reach remedies which, aided by diet, will afford the patient relief, we would certainly all be glad to know it.

Dr. HEMMETER—I must say that I am very much pleased at the discussion of this paper and at the questions which have been asked. One question was whether or not maltose is absorbed from the human stomach and enters the blood as such. I have invented a method of studying this problem by plugging the pyloric end of the stomach in animals; maltose is then introduced into the stomach. The pylorus being closed by the plug, it can not escape into the intestines. Nevertheless, shortly afterward there is no maltose left in the stomach. It is absorbed into the blood through the walls of the stomach. As Dr. Stewart has said, Sir Wm. Roberts has shown that maltose can be absorbed directly into the blood. Not only maltose, but albumose may be absorbed, and I have no doubt that egg albumin may be injected into the intestine and be absorbed directly into the blood without being digested at all. I have been asked how long amylosis will go on in the human stomach after an ordinary meal. Now it is limited by only one thing, that is, the change to an acid reaction in the stomach contents. If the food stays long enough and there is not too much acid, the starchy constituents will be entirely converted in the stomach. In dilated stomachs, where there is destruction of the hydrochloric acid cells, the digestion of starch may go on for many hours. As soon as the proportion of hydrochloric acid reaches 0.15 then the action of starch ceases. This generally occurs on the average in about forty minutes after the close of an ordinary meal, so that we have this length of time in which to digest the starchy portions of our food in the stomach. If too much work is thrown upon the amylolytic action of the intestinal glands, there may be intestinal failure and intestinal indigestion. Because the amyllopsin of the pancreatic juice digests starch and the ptyalin of the saliva digests starch, we must infer that their

actions or end products are the same. The cases which Dr. Murdock has mentioned and in which we find alternating states of the secretion, one day hyperchylia, the next achylia, and perhaps in the next few days hyperchylia again, have been termed by me *heterochylia*. In determining the degree of acidity in these cases it is essential to know the amount of proteid in the test meal, because the secretion of HCl is greater after proteid than after amylaceous foods. The condition causing heterochylia can only be cured by correcting an underlying neurasthenia, by good hygiene, proper diet, electricity, baths, etc. Moreover, I believe that in many of these cases, lithemia and gout are at the bottom of the condition of heterochylia. In cases where this persistently exists, the patient may be taught to pass the stomach tube and wash out the stomach for himself with diluted HCl or alkalies as may be indicated, but it is impossible to go into the details of the treatment or give any sweeping advice for the management of such cases.







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DISEASES OF THE GASTROIN-  
TESTINAL TRACT ON THE  
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Reprinted from the MEDICAL RECORD  
November 16, 1907

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WILLIAM WOOD & COMPANY  
NEW YORK



# DISEASES OF THE GASTROINTESTINAL TRACT ON THE BORDERLAND BETWEEN SURGERY AND INTERNAL MEDICINE.\*

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It has been a great pleasure to me to have been able to participate, in however trifling a degree, in the proceedings of this Association, which I look upon as a prominent acknowledgment of a principle which is daily forcing its way among us, and which is destined to play an important rôle in the future history and development of American medicine. I mean the interchange of clinicians and surgeons between medical organizations and universities in different States of our Union; and through them the dissemination of the various aspects and view points of medical problems as they present themselves to clinicians and surgeons in the various sections of this great country.

Upon the suggestion of that most brilliant of all monarchs, the German Emperor, an interchange of professors through Germany and this country is at present taking place, and this academic interchange

\*Address before the Medical Association of Greater New York, April 11, and before the Academy of Medicine at Cleveland, O., May 12, 1906.

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will lead to a better understanding between the two nations than any principles of politics or diplomacy could accomplish. The highest thoughts of a nation are by no means embodied in those affairs that we call political. They are more likely to be represented in the aims of science, and in the principles of that science whose chief object is the preservation of human life.

By the interchange between our States we shall reach a better understanding of the various diseases occurring, as they do, over latitudes that are far greater than the territory of Europe; but one of the greatest prospects to be hoped for is a better understanding between the internist and the surgeon. Of the former we expect the most refined development of the physical methods of examination—percussion, auscultation, palpation, etc.; a more perfect control of the chemical and microscopical methods of diagnosis, and a deeper knowledge of pathophysiological processes; an exhaustive familiarity of the signs and symptoms of disease. All this in the nonoperating clinician on the one hand, and on the other, of the surgeon, the operating clinician, we expect an exhaustive knowledge of regional anatomy; of the many mechanical and physical appliances to aid in the recovery of objective lesions, and a masterly control of technique with all its collateral, chemical, and bacteriological detail.

Between these two domains of internal medicine a cordial understanding is necessary. What we hope for from the internist is not habitual prejudice against operation, not an exclusive and invariable expectant and conservative method of approaching the abnormal phenomena of life; and what we hope for from the surgeon is not invariably to advocate operation; but the attitude in both from which most progress is to be hoped for, is *cooperation*. Oper-

ative technique is in a ceaseless state of progress. The surgeons have the advantage that the statistics of operation and the indications and contraindications to operation generally incite extensive discussion. Such elements of surgery are more apt to cause the liveliest interest, not only of the medical profession, but of humanitarians at large. But the internist need not be discouraged at this, for I can say, for the American surgeon at least, that although radical and extreme positions and views have occasionally been announced, they have always been willing to recede from too dogmatic a position, when the untenability of it was demonstrated by a broad experience and conservative critical judgment. Thus the internist has lived to see that diseases which were at one time claimed to be only proper for the surgeon to treat, and that the internist was out of his latitude when attempting to treat them, have been conceded back to him, partially at least. Thus we have it from surgeons of very broad experience that appendicitis need not always be operated upon. They admit the possibility of permanent recovery without removal of the appendix. Such a distinguished surgeon as Treves condemns the operative replacement of the kidney for nephroptosis. Kehr, the greatest gallstone surgeon we know of, concedes that there are forms of cholelithiasis where the operation cannot cure the disease; it may become absolutely necessary to remove the gallstone (or stones), but this does not necessarily cure the abnormal hepatic metabolism which leads to gallstone formation. And in the following I hope to be able to present the evidence that even tuberculous peritonitis may be permanently recovered from under conservative or expectant treatment, although at one time laparotomy was considered the only chance the patient had for recovery.

#### THE EARLY DIAGNOSIS OF CARCINOMA OF THE INTESTINE.

In early diagnosis of intestinal cancers we must consider theoretically at least two stages: (1) the latent stage, (2) beginning of manifest symptoms. Concerning the first, the latent period, an early diagnosis cannot seriously be considered possible in the present state of our knowledge. Let us assume that a serum reaction for carcinoma had been made feasible as a result of revolutionizing research into the pathology and etiology of cancer. It seems to me that we are not far from a serum diagnosis of carcinoma by means of which we can recognize this disease even before manifest symptoms have occurred. But even if such an early diagnosis could be made on apparently sound individuals for the time being, great difficulties would stand in the way of reaching an early diagnosis, for who cares for his health as long as the admonishing voices of definite disease symptoms do not compel care. Rectal carcinomata lend themselves most readily to an early diagnosis in the second sense—that dating from the first manifest symptoms. My own private cases of rectal cancer during the last fifteen years number sixty-six. Of these forty-eight cases did not consult me nor any other physician until four months had elapsed after the first symptoms appeared. On the average five months had elapsed since the beginning of the first symptoms, before my cases consulted me. There were fifteen cases that came before three months had elapsed, but only ten of these were found proper cases for operation, and of these ten only six lived two years after operation and then a recurrence of cancer took place. Of eighty-four cases of rectal carcinoma (1896-1905) Boas states that sixty-two did not appear before him for

relief until at least three months had elapsed since the first symptoms. On the average there was a loss of time of six months. Of only nine cases that came before less than three months had elapsed, four could no longer be radically operated upon, and two had passed the period of a feasible operation.

*Carcinoma of the Colon.*—In thirty-six cases of carcinoma of the colon the clinical history showed a record of intestinal diseases of two years in fourteen cases; of chronic colitis of four years in two cases. In two cases the symptoms characteristic of obstruction were existing six and seven years respectively, and in three cases the patients asserted they had obstinate constipation and occasional severe colitis for seven, eight, and nine years respectively. In fifteen cases the most searching inquiry failed to reveal any reliable data for the beginning of the intestinal difficulty.

The majority of cases, even of those that come to the clinician early, do not yet come early enough. *The prospects for early diagnosis of intestinal neoplasms are not favorable at present. The time for early diagnosis is beyond the limit of recognition of patient and diagnostician.*

*Carcinoma and Sarcoma of the Duodenum, Ileum, and Jejunum.*—From records of private practice I am able to report sixty cases of carcinoma and sarcoma of the duodenum, ileum, and jejunum, occurring during the last five years and in the clinical history of which there is a record of the time that elapsed between the appearance of the first noticeable intestinal symptoms and the time at which medical advice was sought.

Average time from appearance of first symptoms to consultation of physician: In twelve cases of



carcinoma of the lower ileum, six months approximately (six months ten days to six months and eighteen days).

In twenty cases of carcinoma of the ileocecal valve, cecum, or end of ileum, four months.

In eight cases of carcinoma of the duodenum, extending from the pylorus or gallbladder, two months two weeks.

In eleven cases of carcinoma of the stomach with metastases in jejunum, ileum, and mesentery, average time, three months one week.

In one case of sarcoma of the ileum and splenic flexure of the colon, three months.

In eight cases of carcinoma of the upper ileum with metastases in the jejunum and mesentery, four months and two weeks.

*Résumé.*—We have before us, therefore, sixty-six cases of rectal cancer, in forty-eight of which the patient did not consult me or any other physician until four months had elapsed since the first noticeable symptoms had become manifest.

Taking them as a whole, five months had elapsed on the average before these patients had consulted me, and even of those who consulted me before three months had elapsed, only ten were operable; and of those ten only six lived two years after the operation.

In thirty-six cases of carcinoma of the colon, twenty-one cases had symptoms of severe intestinal abnormalities existing from two to nine years prior to their consulting me.

Of sixty cases of cancers of the small intestine, the average time from the appearance of the first symptoms to the consultation with the physician varied according to the situation of the cancer. In twelve cases of carcinoma of the lower ileum, this period was six months and fourteen days. The other dates

are given above. Here we have a total of 162 cancers of the intestine as they present themselves in private practice, all coming too late for an early diagnosis and arriving at a time when the most enterprising surgeon would decline to do anything more than an exploratory laparotomy.

In the present state of our knowledge, therefore, the time of the early recognition of carcinomas of the digestive tract is so problematical that it will only exceptionally be possible. It is, therefore, of utmost importance that the researches of a biological and pathological nature aiming towards a serum diagnosis of malignant tumors should receive the encouragement of endowed institutions for medical research. I will have to refer the reader to previous publications on this subject for a more complete elucidation of the direction this form of investigation should take.<sup>1</sup>

#### CURABILITY OF TUBERCULOSIS OF THE PERITONEUM WITHOUT OPERATION.

In 1862 Spencer Wells operated upon a peritoneal tuberculosis owing to a diagnostic error, and for the first time a cure was observed to result from this treatment. Then followed König,<sup>2</sup> whose published observations caused a sustained preference for this method of treatment, and the following three publications, by Lindner<sup>3</sup> in 1892 with 205 cases, by Roersch in 1893 with 358 cases, and by Adossides<sup>4</sup> in 1893 with a report of 405 cases, give account of a total of 968 cases treated in this way. A number of these cases of tuberculosis peritonitis cured by laparotomy were seen at a second operation undertaken for some other cause, on which occasion the peritoneum could be thoroughly inspected and was found free from adhesions and perfectly smooth. The observations had the effect that the majority

of surgeons and even of internal clinicians formed the opinion that laparotomy was the only effective treatment for this disease which otherwise would be fatal.

The question for the thinking clinician to decide is whether a tuberculous peritonitis, not treated by laparotomy, is really as malignant, whether its prognosis is actually as bad, as has hitherto been believed. In this connection it would be instructive to learn what the experience of representative clinicians in Europe and this country has been on this subject.

Nothnagel,<sup>5</sup> after emphasizing that the curability of tuberculous peritonitis has been demonstrated by operative observation, does not doubt the possibility of spontaneous cure.

Naunyn, in his lectures, expresses himself as follows: "The prognosis in the majority of cases is bad, but spontaneous cures and improvements are not as seldom as other authors assume." He adds: "Only a small fraction of our cases have been transferred to surgical treatment."

Strümpell<sup>6</sup> holds that the prognosis of tuberculous peritonitis is absolutely unfavorable; in a few weeks or months a fatal end occurs. In some cases, however, a favorable result occurs in chronic tuberculous peritonitis, or at least a very evident improvement. This cure is only apparent, not an enduring one, for later on the tuberculous process occurs anew in some other organ.

Henoch<sup>7</sup> recommends that the peritoneal tuberculosis of children should be treated by laparotomy, in view of the "hopelessness of any internal therapy." If, in rare cases, a cure results by internal treatment, he considers that they were really not cases of tubercular peritonitis, but some simpler type of chronic peritonitis.

Pribram<sup>8</sup> reports spontaneous improvements which in rare cases have been followed by permanent cure.

Kussmaul<sup>9</sup> describes the case of a young girl with tuberculous peritonitis and incessantly swollen belly, who recovered spontaneously in spite of very impoverished environment.

The surgical and medical treatment of tuberculosis of the peritoneum is very ably compared by E. Graser,<sup>10</sup> but while the results of laparotomy are placed in a brilliant light, the results of conservative treatment are not compiled. The possibility of spontaneous recovery from the disease is, however, mentioned.

H. Braun,<sup>11</sup> in an article on tuberculous peritonitis, says the only successes possible are to be attributed to laparotomy. He does not doubt that spontaneous recoveries may occur, but this fact is not emphasized.

*Classification.*—The expressions used in classifying the different forms of peritonitis differ according to the view point of the observer making them. Thus we can already see in the literature of this subject three kinds of classifications of peritonitis, according to the standpoint of (1) the internal clinician, (2) the surgeon, and (3) the pathological anatomist. A favorable classification among surgeons is into three forms of peritonitis: (1) the simple exudative form or ascites; (2) the dry or adhesive form, and (3) the ulcerative and purulent form. According to König and Roersch laparotomy is capable of curing all three forms under certain conditions, but other surgical authors do not share this opinion. Pic recommends laparotomy only for the fibrous form with or without ascites, and Frank<sup>12</sup> found a mortality of 100 per cent. in the ulcerative purulent



form of tuberculous peritonitis, seventy-four per cent. in the adhesive dry form, and thirty-four per cent. in the exudative form. The anatomical classification is beyond doubt the most exact and had best be considered under two headings, (1) acute and (2) chronic forms of peritonitis; under each of these there are several subdivisions.

*Acute Forms of Peritonitis.*—(1) Circumscribed, nonpurulent peritonitis. (2) Circumscribed, purulent peritonitis (abscess of the abdominal cavity). (3) Progressive purulent peritonitis: (a) Fibrinopurulent, (b) purulent, (c) gangrenous or ichorous form.

*Chronic Forms of Peritonitis.*—(1) Serous or serofibrinous peritonitis: (a) Purely serous, (b) partially adhesive, (c) diffusely adhesive form. (2) Purulent peritonitis: (a) Encapsulated, (b) diffuse chronic, purulent peritonitis. (3) Neoplasms of the peritoneum: (a) Tuberculous peritonitis, (b) benign neoplasms, (c) malignant neoplasms.

Neither the surgical classification above mentioned nor the pathologico anatomical classification can be followed by the clinical internist, for both of these classifications require in most cases that the peritoneal cavity of the living or dead body shall be opened before the diagnosis can be made. *The internist, however, is restricted to methods of physical and chemical diagnosis and the symptomatology of the case.* In a consideration of tuberculosis of the peritoneum, like the present, from the viewpoint of the internist, especially when the object and purpose is to demonstrate the possibility of a cure of this disease by nonsurgical methods, one has to be prepared to meet the objection that any given case of peritonitis which he cures may really not be tuberculous. In the following I will endeavor to give my experience in differentiating the different

forms of peritonitis, but I wish to emphasize right here that *it would be very unfortunate for internal medicine if the clinician were allowed to diagnose only those diseases that could be objectively demonstrated to the eye.* The surgeons are given the opportunity for what might be called "an autopsy during life," but in defense of the purely clinical methods of the internist it should be said that the operative era has been of especially great value for the diagnosis of peritoneal tuberculosis, inasmuch as the operators have proven that tuberculous peritonitis is too seldom diagnosed and that it never is absent when the internist suspects it.

*Clinical Types of Peritonitis.*—In enumerating the various forms of peritonitis that might be confused with tuberculosis of the peritoneum I will, for the sake of brevity, pass over those forms of inflammation that are due to infection (1) through the genital tract in the female perioophoritis, perimetritis, (2) from the digestive tract, perigastritis and perityphilitis, (3) from the biliary apparatus, pericholecystitis, etc. There are forms of peritonitis also which occur secondarily during the course of chronic heart and kidney affections. These will also be passed over.

The more important left then are the following:

1. When peritoneal tuberculosis gradually develops with the clinical picture of simple ascites it is sometimes difficult to distinguish from the ascites due to cirrhosis of the liver. Both diseases may occur together. I have personally observed a case of peritoneal tuberculosis associated with typical hepatic cirrhosis. In those cases the diagnosis is extremely difficult.

2. Infectious diseases like measles, typhoid fever, and dysentery are sometimes found associated with ascites. Cases are on record where an ascites occurring during the course of measles was operated

upon and the entire peritoneum was found covered with miliary tubercles.<sup>13</sup>

3. Malignant tumors of the peritoneum, intestine, gallbladder, or pancreas may be very difficult to differentiate from the tumor form of tuberculous peritonitis. For a distinction between such cases reference must be had to special works on the intestine and peritoneum. (Nothnagel, Hemmeter.)

4. There is a type of ascites that occurs in young girls during the period of adolescence called by French authors "*ascite des jeunes filles*." This is not due to an inflammation but is supposed to be caused by hyperemic and hypersecretory conditions of the peritoneal regions approximate to the inner genitalia. It disappears spontaneously after the first menstruations have occurred.<sup>14</sup>

5. Traumatic peritonitis. Chronic exudative peritonitis that is not tuberculous may occur after injuries to the abdomen. Cases of this type have been described by Henoch.<sup>7</sup>

6. In 1884 Curschmann<sup>15</sup> described a chronic inflammation of the peritoneum of a very peculiar type and of nontuberculous nature which he entitled "*Chronic Fibrous Polyserositis*." It is always associated with a perihepatitis of the same peculiar type, giving the peritoneal and abdominal organs the appearance of being enclosed in a cast of opaque sugar "*Zuckergussleber*," "*Zuckerguss der Serosen*." The cause of this condition is not known. It has been observed after various infectious diseases and after circumscribed forms of peritonitis (cholelithiasis and perityphilitis). Curschmann states that the disease is characterized by two features, namely, a much reduced small hard liver, cylindrical at its edge, and a very protracted course, lasting from two to sixteen years. A distinction between this disease and tuberculosis of the peritoneum would be very

difficult if no other signs of tuberculosis were in evidence, but this so-called Curschmann's disease is so rare that the diagnostician will not often be required to make this distinction.

7. Idiopathic chronic peritonitis. If we deduct from all possible forms of peritonitis those that are due to inflammations starting from the internal abdominal organs, those due to cirrhosis of the liver, to malignant tumors, to traumatic influences, the ascites in young female children and the chronic fibrous polyserositis, very little is left for the so-called idiopathic form. I have never seen a form of this type and doubt its occurrence, and I agree with Nothnagel, who states that the demonstration of a genuine primary idiopathic peritonitis has not yet been given. All of the cases that could possibly be classed as idiopathic would, in my opinion, be found to be tuberculous if some of the exudate were injected into the peritoneum of guinea-pigs or if the tuberculin test were made. Pribram<sup>8</sup> found among 3,500 autopsies by Chiari 165 cases of chronic peritonitis, but not a single one of them could, in his opinion, be designated as chronic idiopathic peritonitis without tuberculosis.

*Differential Diagnosis.*—In speaking of the diagnosis I shall not attempt to give the objective and subjective signs and symptoms that characterize all the forms of peritonitis which I have mentioned in the preceding, but simply emphasize three methods by the aid of which we are enabled to determine at least what is a tuberculous peritonitis and what is not. They might almost be called specific reactions for tuberculosis. These are:

1. Introperitoneal injection into guinea-pigs of some of the peritoneal exudate. In three of the cases in my experience this method has helped us materially to make the diagnosis absolutely certain.



I would suggest in doubtful cases to have the exudate drawn from the most dependent (lowest) portion of the peritoneal cavity, because the success of the infection in the guinea-pig depends upon the presence of the tubercle bacillus in the exudate; and one is more likely to get the bacilli in the pelvic portions of the peritoneum if the patient has been in the erect position for eight to ten hours.

2. Injections of tuberculin (Koch). With this material I have had a very extensive experience, having used it very often since 1890 for the diagnosis and treatment of pulmonary, gastric, and intestinal tuberculosis. In my work on diseases of the intestines (Chapter of Ulcers), I have described a case of tuberculous ulcer of the rectum which was diagnosed and cured by the injection of tuberculin, it being possible to observe the cure by inspection through the proctoscope.

3. The diazo reaction of Ehrlich. This has, in my experience, been a very valuable aid to secure a diagnosis in doubtful cases. If the diazo reaction is very decided and occurs repeatedly during several weeks, one has a right to suspect that any enlarged gland or abdominal tumor or peritonitis is due to a tuberculous process. A patient in my practice (female), aged thirty-eight, consulted me for severe abdominal pains and symptoms of obstruction. A tumor was palpable in the right iliac fossa that might have been mistaken, and was at first considered an appendical tumor. The diazo reaction was repeatedly found and an operation advised. Prof. L. McLane Tiffany found a tuberculous tumor of the colon involving the iliocecal valve, and at the same time there was a general tubercular peritonitis, but the tumor itself was not due to the tuberculosis of the cecum, but to a large caseous conglomeration of glands in the omentum.

It is usually considered that a very evident diazo reaction is indicative of a very bad prognosis in pulmonary tuberculosis, and that such patients should be excluded from treatment in public institutions for tuberculosis. In cases of peritoneal tuberculosis, however, a very strong diazo reaction, lasting for six and even for eight weeks, need not necessarily be a cause of hopelessness, for such cases have been known to become very much improved, and even free from fever. There are cases of peritoneal tuberculosis on record which in spite of the diazo reaction, were cured by the conservative method, and remained cured for two and four years. The reliability of the diazo reaction is doubtless limited; typhoid fever, sepsis, miliary tuberculosis, and other conditions mentioned in most of the works on clinical chemistry, must be excluded; but if the yieldings of the first two methods support the diazo reaction there can be no doubt as to the existence of tuberculosis.

I have compiled eighty cases of tuberculosis of the peritoneum from the statistics and clinical records of the Hospital of the University of Maryland, Bayview Hospital, and from consultation and private practice. Twelve of these cases did not occur in my own private practice, but were seen by permission of other physicians, yet could be studied with sufficient thoroughness to definitely establish a diagnosis of peritoneal tuberculosis, not only from the clinical history, the results of physical examination of the lungs, but also one or more of the objective methods referred to in the preceding.

The question for us to decide was whether any so-called cure was possible by conservative or expectant treatment; and secondly, whether operative treatment could accomplish anything more and give evidence of any better results than the conservative

treatment. In the American literature on the subject of prognosis of tuberculosis of the peritoneum, these two points are by no means satisfactorily investigated. There is a compilation of 357 cases collected from literature in the Johns Hopkins Hospital Reports, Vol. II., but there is no effort to ascertain the comparative merits of the operative and the conservative treatment of this disease of the peritoneum; nor could I find this point considered in our standard textbooks on the Practice of Medicine by American authors. Without going into a detailed quotation of American authors on this subject, it can be said that up to the year 1900, at least, the great majority held the view, and still holds the view, that tuberculosis of the peritoneum is almost always fatal unless treated by laparotomy. Even the most conservative internist shared the view of the surgeon that laparotomy gave decidedly better results than conservative treatment. In fact, at one time this operation was almost looked upon as a specific means of cure. It was, therefore, very astonishing to learn of the views of a prominent surgeon, in which he emphasized the possibility of spontaneous cure of tuberculosis of the peritoneum more emphatically than any internist had ever done before. I consider this contribution so important that I will give a condensed abstract of it in the following:

Borchgrevink<sup>17</sup> found that those cases of tuberculous peritonitis healed most readily in which he found the tubercles already in a process of healing during laparotomy, and vice versa. He describes (p. 439) a primary healing of tubercles during which they disappear entirely, without leaving a trace on the peritoneum. This is the rule in peritoneal tuberculosis, and caseation of the tubercle is the exception. In the tissue of the serosa the growing tubercle produce a histological and physiological reaction

that leads to proliferation of connective tissue cells and the appearance of leucocytes in varying numbers. Thus the serosa swells up around the tubercles which apparently sink deeper and deeper into the surface of the peritoneum. Eventually an organization occurs in this proliferation, most pronounced in the most superficial layer, and later a microscopical examination shows no tubercle bacilli nor giant cells. They appear as small fibroid nodules, but sometimes may yet produce tuberculosis when inoculated into guinea-pigs (p. 441). A simple (idiopathic) chronic peritonitis independent of tuberculosis does not exist, according to Borchgrevink. In six of his cases that were formerly sound with no hereditary history of tuberculosis, no tuberculosis of other organs, and that healed readily and definitely, it was proven that they were tuberculous after all, because the infectiousness of their exudate for guinea-pigs was shown by inoculation.

Laparotomy, according to Borchgrevink, exerts no healing influence on tuberculosis of the peritoneum (p. 446). The reported cures attributed to operation were in reality due to the spontaneous healing already described. Borchgrevink, therefore, rejects laparotomy as a curative means for all cases of tuberculosis of the peritoneum (p. 450).

The description of the resolution of the peritoneal tubercles in this article is given with all the evidences that usually reveal a complete mastery of the pathology of this subject. The account of the retrograde metamorphosis of tubercle stamps Prof. Borchgrevink as a very thorough surgical pathologist. He reports a clinical material of forty-four cases, and in addition three cases of perforation peritonitis. Of these, one-half, or twenty-two cases, were operated upon, and one half were treated by the conservative or expectative method. In the cases that were



treated by operation there were sixty-four per cent. of cures, and among the cases that were treated by the conservative method there were eighty-two per cent. of cures. Of those eighty-two per cent. of spontaneous cures there were forty-one per cent. that remained lastingly sound and well; namely, were reported well one to two years after they left his observation. A further twenty-seven per cent. were well two years after; so there are really sixty-eight per cent. of cures which lasted over one year as a result of the conservative treatment.

Borchgrevink is a surgeon, and it is therefore so much the more surprising that he should absolutely deny any curative effect to laparotomy in tuberculous peritonitis. My personal experience and opinion is that this view of Borchgrevink, while perfectly justifiable, if deductions are made only from his own cases, is too sweeping a view, if we should apply it to the results of our American surgical statistics of laparotomy for tuberculosis of the peritoneum. For although there may be a smaller percentage of cures after laparotomy for this disease, one cannot fail to recognize that there are a great many cases in which marked improvement followed, though here again one has to decide how much of the improvement is due to the laparotomy itself and how much is due to the favorable conditions of hospital environment and to the normal processes of repair.

As was said above, of eighty-two per cent. of Borchgrevink's spontaneous cures, forty-one per cent. were reported perfectly sound one to two years; and twenty-seven per cent. two years after they left his hospital; all in all sixty-eight per cent. of cures lasting over one year. This brings me to define what is meant by a permanent cure in operative and nonoperative cases. We should at least require that a case has been *observed by some reliable*

*physician and reported well one year after the laparotomy or after the conservative course of treatment before we should feel justified in classing such a case among the cures.* I have observed in numerous American reports on operative cures of this disease that the writers do not speak of the length of time during which the after history of the operative case was controlled and reported by a physician. In the German reports by surgeons, the same objection can be urged against the great majority.

In an article on "Surgical Tuberculosis of the Abdominal Cavity," with special reference to tuberculous peritonitis, William J. Mayo<sup>18</sup> does not state definitely how long he had observed his cases of tuberculous peritonitis after this operation. In one place he states that since January of this year, meaning January, 1905, he operated on sixteen cases of tuberculous peritonitis; but as the article is published in April, 1905, this does not leave a sufficient time to speak of a cure in the sense of the term as it has been defined above. In another place Mayo asks the question, "Can we prevent a relapse?" and answers, "Certainly we can in many cases," and then continues, "Of twenty-six radical tubercle operations we have made on cases of tuberculous peritonitis, twenty-five recovered, and of these seven had been operated on by simple laparotomy one to four times previously; in not a single patient as yet has another operation become necessary." While this paper of Dr. Mayo is unusually meritorious because it emphasizes the necessity of seeking out the source of infection, either the appendix, the cecum, or the tubes and ovaries in women, and that a cure is more likely to follow if reinfection could be prevented by removal of the original portal of entry, it leaves us in doubt regarding the main condition upon which a claim of

a cure can be made; namely, the time during which the patient was authentically observed after the operation. Mayo thinks the failure of simple laparotomy and evacuation of the fluid exudate in tuberculous peritonitis to maintain a high place in surgery is due to reinfection from lesions in the mucous membrane of the Fallopian tube, appendix, or some part of the intestinal tract. He admits, as is undoubtedly true, that the original infecting lesion can many times not be discovered, and that not all cases of reinfection can be explained by overlooking of the original source of infection. Mayo also admits that expectant or conservative treatment may many times cure the primary lesions by aiding a natural process of cure which I have described in the preceding.

We have here a fair-minded surgical presentation of the subject, which endeavors to do justice to the possibilities of cure that may come from a purely conservative treatment. We shall not reach the real truth as to which is the most expedient and correct course to pursue in the treatment of tuberculous peritonitis by asking whether we are to treat them all surgically or all by the expectant or conservative method. Put in this manner, the proposition with which we have to deal could not be settled except in an unsatisfactory and dogmatic manner. The surgeons should, personally and individually, convince themselves of the spontaneous natural cure of tuberculosis of the peritoneum, to be impressed with capabilities of the normal forces of the body tending towards recovery (phagocytosis, opsonins, etc.), and in any given case be guided by accompanying conditions. For instance, I have known a number of cases operated upon that terminated fatally because the vital resources of the patient were too exhausted to overcome the effect of

the narcosis and laparotomy. From the condition of the peritoneum I formed the idea that if the laparotomy had been postponed and executed, say a month later, the patient might have recovered.

The internist, on the other hand, should not gain the impression from Borchgrevink's work, nor from my experiences, as stated herein, that conservative medical treatment will always and under all conditions give better results and a larger number of cures than surgical treatment. There are cases of tuberculosis of the peritoneum which should always be operated; that is, as soon as certain accompanying constitutional signs and symptoms are evident, a laparotomy should be done. The rules that should serve as guiding lines to determine which cases should be operated and which should not, can only be determined by very large and objective experience and mature critical judgment.

I am not dealing in this report with acute peritonitis, nor with perforative peritonitis, nor with traumatic nor postoperative peritonitis; but with that form of peritonitis caused by the tubercle bacillus, and I desire that my remarks should be strictly interpreted as confined to this condition. The fact which William J. Mayo points out that removal of the Fallopian tubes effects a more permanent cure of the peritoneal tuberculosis if they constitute the source of infection, is shown in the following results of Adolf Frank,<sup>12</sup> published in 1900.

The conclusions of Adolf Frank are:

1. The best prognosis is met with in operative treatment of the exudative form of peritoneal tuberculosis, with forty to fifty per cent. definite cures.
2. In the adhesive form there is a grave prognosis; only twenty-five per cent. of operative cases are cured.



3. The ulcerative suppurative form has a very grave prognosis.

4. In the exudative as well as adhesive form the best prognosis is found in those cases of peritonitis that emanate from the female genitalia, and which are treated by removal of the adnexæ. In this manner seventy-five per cent. of the exudative, and fifty per cent. of the adhesive form are cured.

5. The attempt to relieve peritoneal stenotic phenomena by laparotomy and enteroanastomosis, appears justifiable, although the results leave much to be desired.

6. Tuberculous fecal fistulæ yield an exceedingly grave prognosis.

7. In ovarian cystomas associated with peritoneal tuberculosis, a definite prognosis cannot be established on account of the deficiency of material.

8. A compilation of nonoperative cases with a view to learning the permanent cures, and also those treated by abdominal puncture or aspiration, is exceedingly desirable.

The greater frequency of peritoneal tuberculosis in the female is undoubtedly due to the greater liability of infection by way of the adnexæ (Murphy, "Tuberculosis of the Female Generative Organs"). That a conservative treatment in such cases is liable to be followed by reinfection is a point in which I must agree with J. B. Murphy, Ochsner, and the Mayos, and it simply shows that this question cannot be decided by castiron rules one way or the other. It is still a subject that is on the borderland between surgery and medicine; yet I should like to formulate three conditions under which a tuberculous peritonitis should not be operated upon.

1. A diffuse tuberculous peritonitis, with high fever, is not a proper condition for operation. Such

patients should be given a chance for improvement under conservative treatment.

2. Diffuse or localized forms of tuberculous peritonitis, with the objective signs of extensive irritation of the peritoneum (irritation meaning sensitiveness, not necessarily inflammation), and with symptoms of intoxication of the entire body. In these the operation should be postponed.

3. A general systemic infection and pronounced weakness should contraindicate the operation.

4. Extensive tuberculosis of other organs (lungs, larynx, liver, pleuræ) is a contraindication for operation.

*Personal Observations.*—Of the eighty cases of tuberculosis of the peritoneum which I could study personally, eleven could not be traced for sufficient length of time to render them available for this report. Of the sixty-nine cases that could be reached by correspondence with their physicians or because they belonged to my own private practice in Baltimore and its environs, twenty were operative. Of these twenty that were operated upon, the following gives the result one year after the date of operation:

John M. C. Diffuse peritoneal tuberculosis; source of infection unknown; laparotomy; living and well fourteen months after date of operation.

Henry H. O. Acute tuberculosis of the peritoneum and pleura; laparotomy; tuberculous appendix removed; well and sound two years after laparotomy.

Miss Elizabeth J. A. Tuberculosis of the peritoneum; no ascites; permanently cured, four years after operation.

Frank D. P. Tuberculous peritonitis; laparotomy; cured and well fourteen months after operation.

Anna W. J. Ascites, tuberculosis of the pleura; apparently cured three months after operation; relapse; pulmonary hemorrhages, fever; second ascites five months after original laparotomy; second laparotomy in Philadelphia; death.

Annie R. Ascites, tuberculosis of the lungs; laparotomy; improvement of six weeks, then double-sided exudative pleurisy and death. Ascites returned two weeks before death.

Miss R. T. Tuberculosis of the lungs, circumscribed fluctuating mass in the abdomen; laparotomy; no improvement; death four weeks after laparotomy.

Mrs. Julian B. F. Tuberculous ascites; laparotomy; improvement for three months, return of ascites at the end of third month, palpable tumor in right iliac fossa; reported second laparotomy in Washington and death.

Mrs. A. C. H. Tuberculosis of the peritoneum, otitis media, tuberculosis of the skin below the right ear; laparotomy; improvement for six weeks; return of ascites, high fever, pleurisy; death.

Dr. A. S. R. Tuberculous ascites; tuberculous swollen knee joint; laparotomy; writes that he is well six months after laparotomy; eight months after laparotomy report of his death from his physician.

Mrs. E. de V. Tuberculous ascites, tuberculosis of tubes and ovaries, fever of  $103.5^{\circ}$ , pleurisy; laparotomy; improvement for three months, then gradual aggravation, pleuritic effusion, which is withdrawn by aspiration; as the pleurisy is recovered from the ascites returns; second laparotomy, removal of tubes and ovaries, which were found tuberculous; death two weeks after second operation.

Mrs. J. H. S. Tuberculous ascites; reports that fluid has already been withdrawn twice by tapping;

supposed cirrhosis of the liver, but positive reaction to tuberculin tests; guinea-pigs become infected with tuberculosis by ascitic fluid, withdrawn; laparotomy; high fever continued; no improvement; death one month after laparotomy.

From the service of Prof. Randolph Winslow, University of Maryland, I am enabled to report the following cases of tuberculous peritonitis that were treated by operation:

E. C. E. Attorney, aged fifty-five; great emaciation, ascites: differential diagnosis between tuberculous peritonitis and cirrhosis of the liver could not be definitely established; laparotomy revealed tuberculous peritonitis; greater omentum retracted and rolled up into a strip; first seen November, 1905; improved after the operation, but lived only two months thereafter.

Miss P. T. Aged fifteen; admitted November 2, 1903; discharged December 1, 1903, very much improved; entered with fever, rapid pulse, distended abdomen and ascites; laparotomy revealed peritoneum studded with tubercles; drainage with gauze for forty-eight hours: there is no record of the length of time this case was observed and known to be well after the laparotomy; she is therefore not counted among the cures. (A recent report gives her present condition as favorable. September, 1907.)

W. M. White, male, aged sixteen years; seen by Dr. Winslow at House of Refuge, Baltimore, August 5, 1900; sent to the hospital of this institution with very high fever, pain in the abdomen; was supposed to be suffering from typhoid fever, and then sent to the University of Maryland; admitted August 11; emaciation, diarrhea, abdominal tenderness, irregular temperature, 99° to 103° F.; still supposed to be typhoid fever; a Widal reaction



was reported positive; a sudden fall of temperature from 103° to 97° caused the suspicion of a perforation; laparotomy revealed tuberculosis of the peritoneum; complete recovery; reported sound and well six years after the operation.

W. R. B. White, female; probably from service of Prof. Frank Martin; tuberculous pleurisy, which was aspirated a year before admission to the hospital; admitted for supposed intestinal obstruction; ascites; laparotomy; tuberculosis of the peritoneum; recovery from operation, but symptoms of intestinal obstruction continued; death six weeks after the operation; intestinal obstruction due to peritoneal adhesions and large tuberculous mesenteric glands.

From the service of Prof. L. McLane Tiffany, of the University of Maryland:

C. J. Colored, female, aged sixty; tuberculosis of lungs, ascites; laparotomy; death within a week thereafter.

M. S. Colored, female; tuberculosis of the lungs, ascites; tuberculosis of Fallopian tubes and peritoneum; laparotomy; improvement; seen four months after operation; death reported six months after operation.

Mrs. J. White, aged thirty-six; ascites; peritoneum studded with tubercles; laparotomy; reported well two years after operation; may still be living.

J. C. McG. Male, white; ascites; tuberculosis of the peritoneum and of the lungs; laparotomy; death four weeks after operation.

From these twenty cases, then, I conclude that seven have been cured by operation, which makes a recovery of a little over one-third of the cases. Seven of the twenty were males and thirteen were females. It is interesting to note that of the seven cures five were in men. These cures did not occur

in my own practice, but in the practice of colleagues, and some of them came from a great distance and lived where surgical help was not near, and I had to depend upon the reports of the physicians in the country for a knowledge of the progress of the case.

Forty-nine cases were treated medically ; I include in this medical treatment the aspiration of extreme ascitic effusion by means of the same apparatus which is used for the aspiration of large pleuritic effusion. Thirty-two of the forty-nine cases treated by the conservative method were reported dead within eight months to one year after they were first seen. Seventeen were reported still living one year after they were first examined for treatment. Five were living three years after the first conservative treatment, two four years after the treatment, six two years after the treatment, and four one year and three months to one year and five months after the first conservative treatment. All in all, this makes seventeen lasting cures out of forty-nine cases treated by the conservative method. This is about one-third of the cases treated medically. While the results are about the same as for surgical treatment, it is necessary to point out that *the duration of the cure after the time of the first medical treatment was much longer in those cases that were treated conservatively than in those cases that were treated by operation.*

Koenig<sup>19</sup> claimed that one-fourth of all his operative cases of tuberculous peritonitis were cured. Czerny claimed thirty-eight per cent. of recoveries. Mikulicz and Rotter give forty-three and fifty-six per cent. of recoveries respectively.

A number of the statistics that have been reported, for instance, those of Frank, who give fifty per cent. of spontaneous cure, and those of Pic,

who give twenty to thirty per cent. (quoted from A. Rose<sup>20</sup>), are not based upon a sufficiently large number of statistics. While I cannot confirm the results of the Surgeon Borchgrevink that more cases are cured under a purely conservative medical treatment than under operation, nevertheless my experience proves that at least as many cases of tuberculous peritonitis recover under the expectant or conservative treatment as will recover after an operation.

PEPTIC ULCER OF THE DUODENUM AND JEJUNUM  
FOLLOWING GASTROENTEROSTOMY FOR BENIGN  
STOMACH DISEASES (STENOSES).

The digestive act in the human being is so arranged that it occurs in media of varying chemical reactions. It begins in an alkaline, or at any rate, a neutral medium in the mouth. This is the beginning of amylolysis by ptyalin. Next follows a proteolytic action in the acid medium of the stomach. The pepsin of the gastric juice is not active in any but an acid medium, in fact, it forms an unstable compound with the hydrochloric acid. The next portion of the digestive tract is not adapted to the same degree of acidity of contents as the stomach, therefore, we find in the duodenum secretions which contain a great deal of alkali, whose immediate effect is the neutralization of the acid gastric chyme. The bile and the pancreatic juice as well as the intestinal juice of the upper part of the bowel, contain enzymes which are active only in an alkaline medium. If the HCl as it passes through the pylorus is not neutralized the pepsin is still active. The columnar epithelium of the stomach has become resistant to pepsin HCl by a process of adaptation, but this is not the case with the epithelium of the duodenum. If there is free HCl in the duodenum the pepsin will attack the

epithelium. This together with an altered state of the mucosa of the duodenum constitute the fundamental causes of duodenal ulcer. There are other causes, such as toxins circulating in the blood ("sepsin" of Edwin S. Faust, Pharmaceutical Laboratory, University of Strassburg) and also the toxins which result from extensive skin burns, but for our present purpose the above process of pathogenesis is of more direct bearing. We see, therefrom, that nature's purpose is to compel the acid chyme of the stomach to pass the orifices of the bile and pancreatic duct, and above all things that degree of acidity in the stomach should not, for any length of time, exceed two parts per 1,000. If, therefore, in gastroenterostomies for benign obstructions of the pylorus where the gastric juice is active (indeed very frequently it is hyperactive) it becomes necessary to establish an artificial communication between the stomach and the bowel, care must be taken to insure such a course for the food as nature intended it should take, for if the hyperacid gastric contents containing considerable active pepsin, continually pass over a duodenal mucosa, which is already chronically diseased, it is evident that conditions must become aggravated, and eventually duodenal or jejunal ulcer may develop.

My personal experience with such grave consequences of operation has all been in private practice. I have been consulted in the same case many different times, by surgeons who had operated for obstruction of the pylorus several months before, and who were obliged to operate a second time because of the return of intense pains and blood in the stools. I regret that it is impossible for me to publish my personal experience on such cases in full, the reason for this inability being that the particular patients were



not seen often enough and the surgeon in charge preferred to publish the cases at some future period, but my experience does not differ much from that of Tiegel, which I quote in full in the following.

As a representative of that class of clinicians, who are endeavoring judiciously to cooperate with the surgeon, I desire to express the hope that as a result of this symposium there may be an effort on the part of the surgeons to convince themselves by personal investigation of the power for effecting a cure contained in the nonsurgical methods of treatment. This effectiveness of purely medical treatment holds good both before and after operation, even when such operations have become absolutely necessary, for it is possible to reduce the hyperacidity of the gastric juice and to heal a duodenitis and jejunitis.

Max Tiegel<sup>21</sup> reports twenty-two cases. The diagnosis is difficult in chronic cases; a sure diagnosis is impossible. The symptoms are the same as those of penetrating ulcer of the stomach. Medical treatment, because diagnosis cannot be made with certainty, is beset with difficulties. Surgical treatment is even more unfavorable. Of thirteen cases Tiegel states three died immediately after the operation. In eight cases there was a return of jejunal peptic ulcer. Only in two cases was the operation followed by radical cure, and in these two cases a long postoperative observation of the cases is not reported, and as recurrence of jejunal peptic ulcer in some reports is stated as coming on very long after the operation it is necessary to insist on a long observation of postoperative cases. Heidenhain reports a case that was operated upon a second time for recurring jejunal peptic ulcer and studied for four years, during which time he remained free from further intestinal ulcer. Of the recurring je-

jejunal ulcers Tiegel reports two cases operated upon after the gastroenterostomy. In both a jejunostomy was undertaken. The first showed fresh ulcers at the pylorus, the second showed an ulcer at the place of the gastroenterostomy, which ulcer was excised; a jejunal fistula of jejunum was made (*i. e.* a third operation) and the patient was fed for three months through a tube inserted into the fistula. During this time, as well as three and a half months after removal of the tube, the patient was free from complaints. Then followed new symptoms which were found to be due to a new ulcer at the place of enteroanastomosis. The improvement due to jejunostomy was only transient in this case, and Tiegel now advises to discard a subsequent jejunostomy in such types of cases and substitute the digestive process in the stomach by rectal nutrition. Although rectal alimentation has a much inferior value for nutrition it should be preferred, as a transient measure, to a severe operation, very doubtful in its results, especially when one considers that these means and conditions of alimentation during jejunostomy are by no means ideal.

In view of these discouraging results of secondary operations in cases of jejunal peptic ulcers, a longer concession should be made to purely internal treatment. At least a very extensive attempt with the internal treatment should be made before proceeding to another operation. (Bed rest, liquid diet, rectal alimentation, hot external cataplasms, belladonna, alkalies, bismuth subnitrate, nitrate of silver, etc.) The etiology of jejunal ulcer is not uniform. There are three main causes: (1) Effect of gastric secretion retained by contraction of intestine below the point of gastroenteroanastomosis. (2) Circulatory disturbances. (3) Neurotrophic influences.

Dr. Stephen Watts<sup>22</sup> has reported two cases of

peptic ulcers of the jejunum occurring in a dog after gastroenterostomy (published also by Mikulicz<sup>28</sup>). This paper contains an excellent illustration of the condition and analysis of all cases reported in man to that date.

Of peptic ulcers of jejunum observed only after gastroenterostomy for benign disease of stomach, chiefly in males, there are two types: (1) Those that are at first completely without symptoms, then a sudden perforation takes place into the peritoneal cavity. (2) Chronic cases, with severe pains and adhesions to other abdominal organs. These cannot be distinguished from penetrating gastric ulcer and are characterized by great tendency to recurrences.

In the second class the operative results are unfavorable. Treatment by internal therapeutics, rest, and diet is more favorable. Therefore, a purely medical and dietetic treatment, as in gastric ulcer, should be tried for a long time. Acute perforation compels immediate operation.

Posterior gastroenterostomy is less likely to be followed by jejunal ulcers than the anterior type of this operation.

Gastroenterostomy in benign affections (stenoses) of the stomach should be employed less and gastroduodenostomy more, and medical treatment should be more favored after any operation is recovered from, because of accumulating reports of duodenal and jejunal ulcer after these operations. Where an operation is necessary, pyloroplasty (Finney's operation) gastroduodenostomy is to be preferred. After every operation for benign affections of the stomach where a hyperpeptic gastric juice continues to be secreted, strict diet, olive oil, and alkalies should be recommended for a long time. In short, such operated cases should be turned over once more to the

internist for treatment by diet, rest, mineral waters, and such chemical agents as experience and experiments have proven to be of remedial and curative value.

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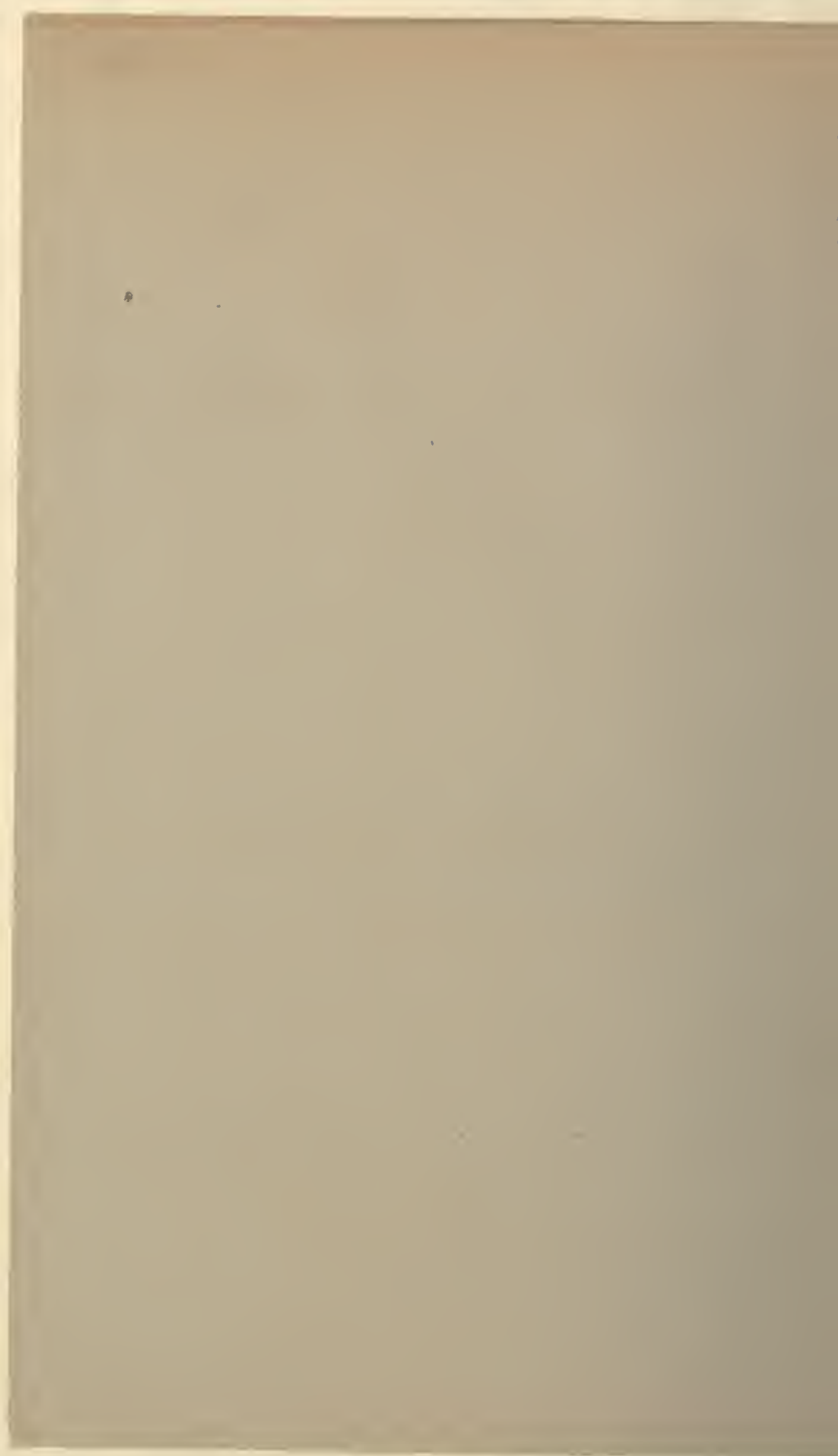
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# JANUS

Archives internationales pour l'Histoire de la Médecine et la Géographie Médicale.

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Treizième Année.

— EXTRAIT. —

1e et 2e Livraison.

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MAJOR JAMES CARROLL

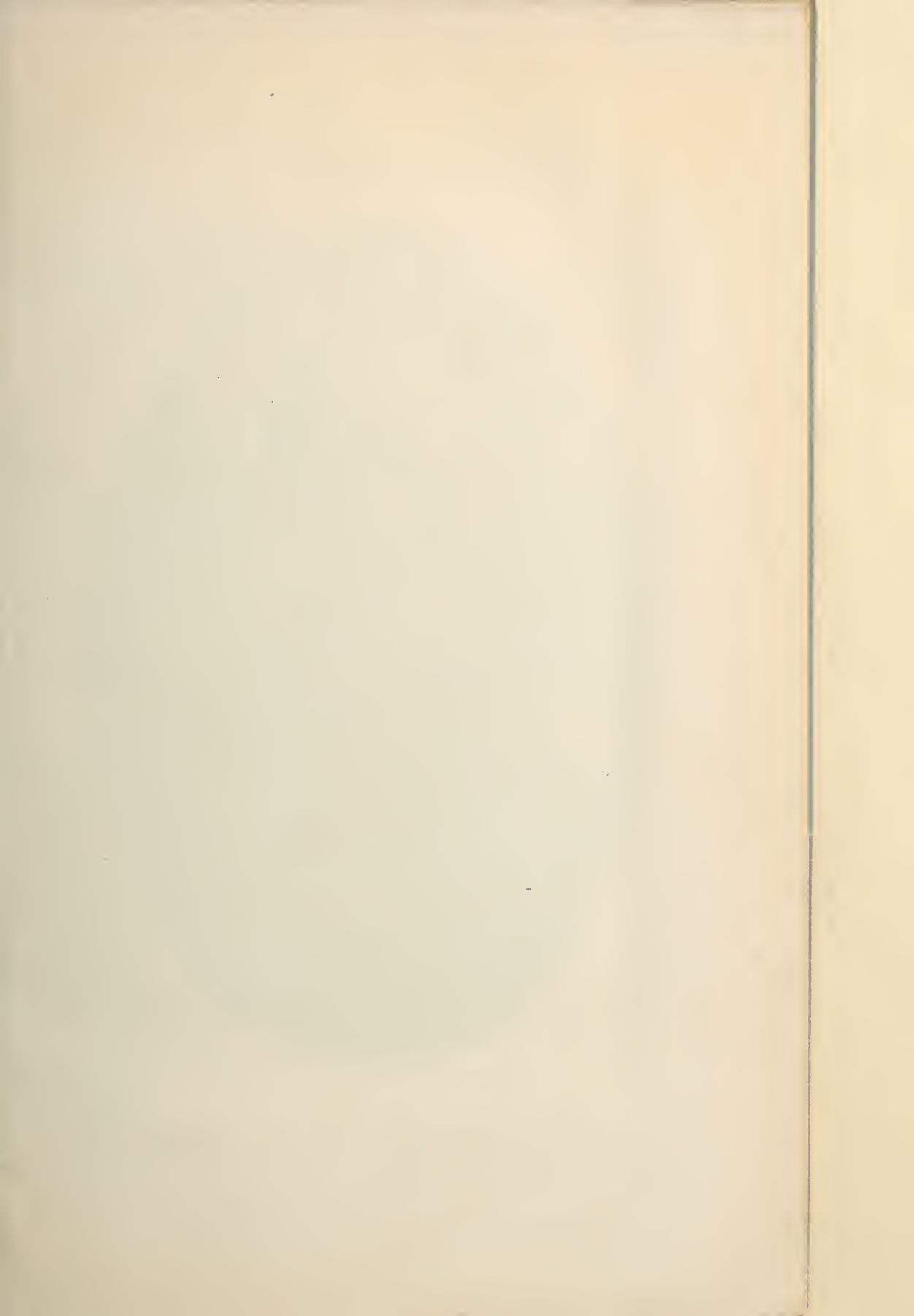
BY

JOHN C. HEMMETER, M.D., Phil. D., LL.D.



HARLEM (HOLLANDE). — DE ERVEN F. BOHN.









## MAJOR JAMES CARROLL

OF THE UNITED STATES ARMY, YELLOW FEVER COMMISSION,  
AND THE DISCOVERY OF THE TRANSMISSION  
OF YELLOW FEVER BY THE BITE OF THE MOSQUITO  
"STEGOMYIA FASCIATA",

BY

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A scientific and medical discovery so far reaching in the blessings it bestows upon the human race, that it is not exceeded in this respect by any other discovery in the history of medicine, has been made by three American Army Surgeons. The names of these three men are Major Walter Reed, Major James Carroll, both Surgeons in the United States Army, and Dr. Jesse W. Lazear, Acting Assistant Surgeon, U. S. A. A fourth member of the U. S. Army Yellow Fever Commission was Dr. Aristides Agramonte, Acting Assistant Surgeon in the U. S. Army, a Cuban by birth and, as I am informed by former Surgeon-General, U. A. S., Geo. M. Sternberg, he was an immune. Dr. Agramonte is the only one of the U. S. A. Yellow Fever Commission, who is still living.

When we consider, that this Commission first came together in June, 1900, all of its members being then vigorous and healthy young men, and that the last American of this Commission, the third to die, departed this life in September, 1907, from the indirect results of a severe attack of yellow fever, experienced seven years ago, we will gain an insight into the severity of the duties of these philanthropic pioneers of American Medical Science. Dr. Jesse W. Lazear died on September 28, 1900. He had been stung on September 13th by a mosquito, which chanced to alight upon his hand. He believed this insect to be a "common ordinary brown mosquito", and not a "*Culex Fasciatus*", but as he permitted this insect to fill itself with his blood, there is no exaggeration in saying, that he knowingly and willingly accepted all the chances of a voluntary inoculation, which brought on a violent attack of yellow fever, that ended his highly useful life in a hospital at Quemados, Cuba. His infection by the mosquito took place in Las Animas Hospital, located in the outskirts of Havanah.

Major Walter Reed, U. S. A. who was the chief of the Yellow Fever Commission, acted as chairman and head of affairs, died on November 22, 1902,

in Washington, six days after an operation undertaken for appendicitis.

Dr. Jas. Carroll, Major and Surgeon, U. S. A., with whom this article deals more especially, died in Washington on the 16th of September, 1907, after a protracted illness, which had given manifestations of a more or less severe character for the last six or seven years. In fact, Carroll told me personally during a banquet, which was given to Professor Paul Ehrlich, of Frankfort A/M, by Professor William H. Welch, of Baltimore, "I have never been a well man since that awful attack of yellow fever in August, 1900".

We may justly conclude, that two of the three American members of this Commission died as Martyrs, and the Chief of the Commission, Dr. Walter Reed, though he was fortunate enough to escape an attack of yellow fever, and as head of the Commission it has been suggested by Professor Welch, was ordered not to submit personally to the sting of the yellow fever mosquito; yet when we reflect, that appendicitis is frequently caused by certain chronic catarrhs and microbic diseases of the colon, acquired especially in the tropics, and by the vicissitudes of an unaccustomed diet, as well as the exposure of travel, we may, without much stretch of imagination, appreciate that the indirect cause of Reed's early death, was the result of his work and exposures, when a member of the U. S. A. Yellow Fever Commission.

No such pilgrimage of three clinicians into a country, infected with a dangerous disease and sealing with their lives a brilliant discovery, is known to me in the entire history of medicine; and in making this statement I do not depend entirely upon my own knowledge, for I have consulted many specialists on the history of medicine; nor is the achievement of these three men, considered either from the purely scientific or from the humanitarian aspect, exceeded by any other single medical discovery, except perhaps the discovery of anaesthesia, which is also an American achievement, or the discovery of protective vaccination by Jenner; or of the Bacillus of Tuberculosis by Koch. The weight of this assertion may be better understood by reading an article published by Reed and Carroll in the New-York Medical Record, October 26, 1901, entitled "*The Prevention of Yellow Fever*". From the statistics there collected, covering a period from 1793 to 1900, there have not been less than 500,000 cases of yellow fever in the United States within that period.

In addition to this we cannot disregard the loss to commerce, interstate and international transportation, and the direct financial losses. It is stated by Horlbeck, Chairman of the Committee appointed in 1897, to investigate the cause of Yellow Fever, that the total loss to the country caused by the epidemic of 1878, was not less than \$ 100,000,000.—

When Karl Lamprecht in his "*Americana*", "Freiburg" I/B states that all the achievements of the American Nation could be wiped out, as if they never had occurred, and still the human race would be none the worse, he makes a disparaging assertion, not in agreement with the great historians of his own country; but certain it is beyond all doubt, that the work of the U. S. A. Yellow Fever Commission has produced a result, viz, the discovery of the transmission of yellow fever by a specific mosquito, the blessings of which will last forever. Nor could Lamprecht at all have been a thorough student of American scientific endeavor, when he asserts that the only outcome of American existence as a nation, so far, has been "a great experiment in democracy".

The facts narrated in the following were obtained largely from Maj. James Carroll himself during many interviews, and from the articles given as references in the text.

For a biography of Major Walter Reed and his scientific work the reader is referred to the volume by Dr. Howard A. Kelly, entitled "Walter Reed and Yellow Fever, New York, 1906". About ten pages of this book are devoted to a brief sketch of the life and work of Major Carroll, and about eight pages to the much beloved and lamented Dr. Jesse W. Lazear, who was a Baltimorean by birth, and a man of exceptional personal magnetism, in addition to possessing rare scientific versatility.

Before and during the year of 1897 there were two views proposed regarding the infectious or causative agent of yellow fever: One was by Dr. (then Major-Surgeon) George M. Sternberg, who in 1897 was a member of the first Yellow Fever Commission appointed by the United States Government. For years Dr. Sternberg, later on Surgeon-General of the United States Army, had made systematic investigations of the bacteriology of yellow fever, in Vera Cruz, Rio de Janeiro, New Orleans and other harbor cities of the south. It was impossible to continue his research after he entered on the duties of Surgeon-General; but as a result of his work up to that time he gained the view, that an organism, the Bacillus "X", was the infectious agent. The second organism proposed as the cause was the Bacillus Icteroides of Sanarelli (Semaine Médicale, Paris 1897, XVII, p. 253).

Professor William H. Welch, of the Johns Hopkins University, has expressed his views concerning the work of Surgeon-General Sternberg, done since the first Yellow Fever Commission was appointed in 1879, as follows, in the Medical News, June 21, 1902, p. 1198:

"His work with yellow fever would stand forever. He said it was a common thing in these busy days to forget the steps, which led up to an



important discovery. All that Dr. Sternberg had done in the study of yellow fever was necessary work, and it had to be done just in the way, that he did it. The ground had first to be cleared; if it were not so the discovery had not been possible, and later discoverers themselves would have had to hunt out the large host of micro-organisms, which Dr. Sternberg had described and laid aside. His careful work practically resulted in the view, that a bacteriological origin of this disease could not be claimed, and it was on apriori grounds, that he himself felt, that Sanarelli's bacillus was not the cause of yellow fever. His study of other's discoveries was most careful and most critical; it was not wasted endeavor".

In the demise of Dr. James Carroll, Surgeon-Major, U. S. A., September 1907, there is lost to Medical Science a most brilliant investigator. Among the many useful men, that have lived, there stand few, whose immense contributions to the welfare of mankind equal that of James Carroll; indeed it can be said, that as an example of keen insight, indefatigable energy and superhuman generosity, this man was peer to any medical pioneer.

The efforts, by which he came to acquire the technical knowledge, which made him famous, are best set forth in a plain simple statement of his early life; and then all may know the ineffaceable trait of perseverance, which characterized every effort in his worthy life, the acceptance of every duty as it came, and the fullest discharge thereof, with constant steady strides towards his goal-achievement.

Major Carroll was born in Woolwich, England, June 5, 1854. His parents were James and Harriet Carroll. His early training was at the Albion House Academy, Woolwich, England, until 1869. In 1874 he enlisted as a private in the U. S. Army, and was progressively promoted to Corporal, Sergeant and Hospital Stewart. Here was created his desire for the study of medicine, and by dint of hard work and perseverance he received the degree of Doctor of Medicine at the University of Maryland, Baltimore, in 1891. In 1888 Maj. (then Sergeant) Carroll married Miss Jennie M. George Lucas, of Cleveland.

After his graduation at the University of Maryland, Baltimore, in 1891, Dr. Carroll studied Pathology and Bacteriology in a special course and post graduate work under Professor William H. Welch at the Johns Hopkins University until 1893. During the summer of this year he worked independently at the World's Fair in Chicago in the Army Laboratory, and it was not until September, 1893, that he met Dr. Reed, in the Army Medical School, Washington, D. C., where he reported by order of Surgeon General Sternberg, U. S. A. At this time Dr. Carroll was Lieut. Assistant

Surgeon, U. S. A., and in this capacity his first great work began. His first order was to assist in the investigation of the statement of Sanarelli, that he had demonstrated the specific etiologic organism of Yellow Fever. This work was done in Cuba in 1897—1902, and with Reed and others he found conclusively the error of Sanarelli, and at the same time disproved Surg. Gen. Sternberg's theory, that the bacillus X was the specific causative factor. Bacillus X of Sternberg was found to be an atypical Colon Bacillus, and that of Sanarelli, the "Bacillus Icteroides", to belong to the hog cholera group. Concerning the publication of these findings, the "Medical News", April 29, 1900, editorily says: "There remains open for ambitious American Bacteriologists a very interesting problem of etiology (referring to the cause of yellow fever), whose study the United States' possession of Cuba and Porto Rico will greatly facilitate, and whose importance can scarcely be overestimated. Any discoveries in the matter will confer lasting fame upon the investigators".

The report of Drs. Eugene Wasdin and H. D. Meddings, of U. S. Marine Hospital Services in an official report: "Report of Medical Officers detailed by authority of President McKinley", adopted the ground occupied by Sanarelli, and proclaimed in their report. "That the micro-organism, discovered by Prof. Guiseppe Sanarelli of the University of Bologna, Italy, and by him named the "Bacillus Icteroides", is the cause of yellow fever."

The work at Quemados, Cuba, of Maj. Reed, Maj. Carroll (then Lieutenant), Dr. Jesse W. Lazear and Dr. Aristides Agramonte, appointed at the suggestion of Surgeon-General Sternberg, as a Board of Army Medical Officers, established by repeated autopsies, that the "Bacillus Icteroides" was, when present, a secondary infection in yellow fever, but was present in neither a single case of repeated examinations of the blood of living cases of yellow fever, nor in the organs at autopsy of fatal cases of a long series of cases, examined by them. Therefore, said they, "Bacillus Icteroides stands in no causative relation to yellow fever, but when present should be considered as a secondary invader in this disease."

At that time there stood rather prominently before the medical profession repeated assertions by Dr. Carlos J. Finlay, of Havana, Cuba, that the mosquito was a possible agent in the transmission of yellow fever. Dr. Finlay had no well defined idea as to the relation of the disease and the mosquito, but suggested, that yellow fever was principally due to an inflammation of the endothelium and intima of the blood vessels, and that the penetration of the proboscis of the mosquito into these vessels resulted in infection of the proboscis, and then an infected mosquito might, by biting a non-immune, mechanically transfer the infection to the party thus bitten.

Drs. Reed, Carroll and Lazear, then (1900), stationed at Columbia Barracks, Cuba, directed their attention to Dr. Finlay's theory (advanced nearly twenty years previously) but as nearly all of Dr. Finlay's experiments to sustain his theory, had been performed in such a loose manner, that it was not proper to attach much importance to them, because his results might have been as well coincidental as rational, certainly nothing had been proved; Professor William H. Welch is of the opinion, that Dr. Carlos J. Finlay's efforts to prove his hypothesis were so contradictory, that they tended rather to invalidate than strengthen his assertions.

Now it appeared to those, who frequently, constantly and freely discussed the possible theories of yellow fever infection, that the disease of yellow fever bore a marked relationship to malaria in that it occurred only, when mosquitoes were present, and under such conditions as suggested, that the organism, whatever it might be, was possibly like malaria, in that it underwent apparently some just such or similar life cycle with the mosquito as intermediate host. To no one in particular of these can all the credit for this idea be given, as it seems, that the frequent daily interchange of ideas was so close, that the resolution to pursue this line of investigation was really an offspring of their conjoined suggestions. Medicine owes to the brilliant discoveries of Sir Patrick Manson and Major Ronald Ross, of the British Army, the first definite knowledge of the part played by mosquitoes in the transmission of malaria, (see Nuttall's paper, Johns Hopkins Hospital Report, 1899; also work by H. A. Kelly, "Walter Reed and Yellow Fever", p. 104—108). Dr. Agramonte, who was stationed at Havana, did not share in these deliberations to investigate in a systematic manner this method of infection. This method involved as a primary step to test, whether or not the disease could be transmitted by the mosquito. This fact, eliminated or established, was determined upon, and with this determination arose the resolution to use human beings as experimental subjects. In order to justify such a responsibility, the Commission, at Carroll's suggestion, determined to show the tremendous risk of self-sacrifice along with whomsoever they could procure among the non-immune for such dangerous experiments.

At this time August 4, 1900, Maj. Reed was recalled to the United States from Cuba, and the real responsibility, both moral and medical, fell upon Dr. James Carroll. Doubtless, had Dr. Reed remained upon the island, he too would have offered himself as did his colleagues upon the altar of self-experimentation in their pursuit of such much needed knowledge. The fact is, however, that he was in the United States, when these tremendous strides towards the light, which revolutionized prophylaxis and hygiene as concerns yellow fever, were made. A year later, in November



22, 1902, that most highly esteemed investigator, Maj. Reed, fell a victim to a fatal attack of appendicitis, and his death, occurring in Washington, D. C. at the time, that this work was going on, and closely following that of the martyr Lazear, and illness of Maj. Carroll, led many of the laity to the belief, that Reed died as a result of yellow fever, inflicted upon himself in the interest of humanity. Such inoculation is suggested by Samuel H. Adam's article in "McClure's Magazine" for June, 1906, where he says, concerning yellow fever, "Lazear died a martyr to humanity and is remembered by one, when the lesser heroes of our Cuba battle-fields are acclaimed by thousands. Carroll barely escaped with his life, and Major Reed, shrinking from no peril, which his companions braved, came through unscathed, by virtue of some natural immunity(?), only to die of another illness the following year." The actual fact, however, remained that, virtually, Carroll was the hero of the hour. It was he, who first proposed experiment on the human being himself; it was he, who offered his arm in the laboratory on August 27, 1900 and permitted Dr. Lazear to apply to it a mosquito, that had previously been known to have bitten four severe cases of yellow fever; it was he, who was at the helm during the crucial hour of the trial; it was he, who first actually demonstrated by positive proof, that yellow fever is transmitted by the "*Stegomyia Fasciata*"; it was he, who later on prevented acceptance of erroneous ideas concerning the specific organism. Although these experiments were continued in a large number of cases after Dr. Reed returned to Cuba to manfully carry out the work, which Drs. Carroll and Lazear had begun, he did not assume the risk of auto-innoculation. In explanation of this, it has been suggested, that he had orders not to do so, as nothing could be further accomplished by such human sacrifice of the Chief of the Commission. So really this most heroic act of self-sacrifice was born in the breast of Carroll, and as his example was so conspicuous it can scarcely be denied, that it served in no small way as an incentive to the many other acts of philanthropic patriotism in the Army to be volunteers for this dangerous service. In truth may it be said, that without this almost incredible self-sacrifice of Carroll, the experiments would have been so hampered, that it is doubtful whether any positive conclusions could have been attained.

The reports of the United States Yellow Fever Commission, because of army rank, bear Dr. Reed's signature as senior officer; and such he was, but Carroll was the man, whose marvelous heroism and accuracy, whose pers'ency, whose indefatigable energy, stood more of the brunt of the fight than any one man — this not to detract in the slightest, however, from the most valuable direction of Reed, and assistance of Lazear and Agramonte.



When Maj. Reed left Cuba for the first time after the initial visit of the Commission to this island (Aug. 4, 1900), Carroll and Lazear began their systematic investigation of Finlay's theory, that the mosquito was the source of infection. Dr. Agramonte, by order of Maj. Reed, was not apprised of this line of work. Dr. Finlay furnished the eggs, from which were hatched the mosquitos first used in these experiments. These mosquitos were kept until maturity free from any source of contamination. The men, who were to be experimented upon, were likewise kept in quarantine, so as to guard against other sources of infection (vomits from yellow fever patients being then regarded as a very dangerous source of infection). Then Dr. Lazear infected nine healthy non-immunes, including himself, with these mosquitoes, which had been allowed to bite yellow fever patients. But either because the mosquitoes had not been kept sufficiently long after their having thus bitten these patients, or had bitten them too late or too early in the course of the disease, no experimental cases of yellow fever developed from these experiments. Dr. Carroll, nothing daunted, then had one mosquito bite a severe case of yellow fever on the second day of the disease, and afterwards three others at intervals of 6, 8, and 10 days, and then allowed Dr. Lazear to apply the mosquito to his own arm, *caused the first experimental form of this disease to be produced, August 27, 1900.* The illness of Dr. Carroll was that of a typical severe case of yellow fever, charts of which can be found in his subsequent reports. (See American Public Health Association Reports 1900.) Throughout this critical illness of Dr. Carroll, Surg. Gen. Sternberg was considerate enough of Mrs. Carroll and her five children in Washington to keep them posted of Maj. Carroll's condition by daily cable. Four days after Maj. Carroll's infection, Dr. Lazear, with four infected mosquitoes, (one of which being the same that was used upon Dr. Carroll), succeeded in producing another case, in a private soldier, who, with full knowledge of the danger, and with free consent, allowed himself to be used in the interest of these experiments.

The following is quoted from "A Brief Review of the Etiology of Yellow Fever", New-York Medical Journal and Phil. Med. Journal (consol.), February 6 and 13, 1904:

"The insect, which had been hatched and reared in the laboratory, had been caused to feed upon four cases of yellow fever, two of them severe and two mild. The first patient, a severe case, was bitten twelve days before, the second, third and fourth patients had been bitten six, four and two days previously, and their attacks were in character, mild, severe, and mild, respectively. In writing to Dr. Reed on the night after the incident I remarked jokingly, that if there were anything in the mos-

quito theory I should have a good dose; and so it happened. After having slight premonitory symptoms for two days I was taken sick on August 31st, and on September 1st I was carried to the yellow fever camp. My life was in the balance for three days, and my chart shows on the fifth, sixth and seventh days my urine contained eight-tenths and nine-tenths of moist albumen. The tests were made by Dr. Lazear. I mention this particularly, because the results obtained in this case do not agree with the twentieth conclusion of Marchoux, Salimbeni and Simond, that the longer the interval, that elapses after infection of the mosquito, the more dangerous he becomes. Twelve days, the period above cited, is the shortest time, in which the mosquito has been proved to be capable of conveying the infection. It is my opinion, that the susceptibility of the individual bitten is a much more potent factor in determining the severity of the attack, than the duration of the infection in the mosquito, or the number of mosquitoes applied. On the day that I was taken sick, August 31, 1900, Dr. Lazear applied the same mosquito with three others to another individual, who suffered a comparatively mild attack, and was well before I left my bed. Thus it happened, that I was the first person, to whom the mosquito was proved to convey the disease. On the 18th day of September, five days after I was permitted to leave my bed, Dr. Lazear was stricken and died in convulsions just one week later, after several days of delirium with black vomit. Such is yellow fever."

Dr. Lazear, while attending to his duties in a yellow fever hospital, was accidentally bitten by a stray infected mosquito (he, while sick, called it an "ordinary brown mosquito"), and fell prey to the disease on September 25, 1900. The attempt to give due credit to the magnificent altruism and genius of these men would lead me to falter in the effort to eulogize their work.

But Dr. Henry D. Holton, in American Public Health Associations, Presidential Address of 1902, struck a sympathetic chord in the hearts of all humanitarian aesclepiads, when he says:

"The patriotism of the military as they spring to the defense of their country, always deserves and receives the applause of the populace. Their deadly conflict on the battlefield is made easy by martial music, the booming of artillery, the rattle of the infantry fire, and the advancing step of comrades. How much more should we recognize the course of such devotees of science as Drs. Carroll and Lazear, who filled with a great philanthropic love for humanity, calmly, quietly, without the cheers or even the knowledge of the multitude, silently submitted themselves to the test to determine in what way this pestilence was communicated. We are told, 'Greater love hath no man than this, that a man lay down his

life for his friend'. We find, that James Carroll and Jesse W. Lazear, fired and impelled by their great love for their fellow men, did offer their bodies as a sacrifice upon the altar of scientific investigation to the end, that in the years to come, hundreds of thousands might escape this pestilential death . . . ."

The practical result of all this work and sacrifice has been evidenced this past summer, not a case of yellow fever has originated in Cuba for the past fourteen months. The quarantine period has been shorter by three months, thousands of lives and multitudes of treasures have been saved, and a feeling of security has filled the communities of the southern portion of the United States.

Dr. Carroll, after his illness, returned to the United States, to recuperate his health, until the middle of November 1900, when he again went to Cuba to continue his work. In the meantime, basing his knowledge upon Carroll's experiments, Dr. Reed published the second conclusion of the Army Commission, i. e., "The Mosquito serves as the intermediate host for the parasite of yellow fever". Amer. Public Health Assoc. Meeting to Indianapolis, Oct. 22—26, 1900.

Upon Dr. Carroll's return to Cuba, he established a camp near Quemados and named it, in honor of his dead comrade, "Camp Lazear". Here he continued his investigations as to the etiology of yellow fever, and in February, 1901, the Commission were able, by such investigation, to establish further valuable data, published as conclusions in "Additional Notes": On the etiology of yellow fever by Reed, Carroll and Agramonte (Journal Amer. Medical Assoc., Feb. 16, 1901.)

"1. The mosquito — *Culex Fasciatus* — or *Stegomyia Fasciata*, serves as the intermediate host for the parasite of yellow fever.

2. Yellow fever is transmitted to the non-immune individual by means of the bite of the mosquito, that has previously fed on the blood of those, sick with this disease.

3. An interval of about twelve days or more after contamination appears to be necessary before the mosquito is capable of conveying the infection.

4. The bite of the mosquito at an earlier period after contamination does not appear to confer any immunity against a subsequent attack.

5. Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease.

6. An attack of yellow fever produced by the bite of the mosquito confers immunity against the subsequent injection of the blood of an individual suffering from the non-experimental form of the disease.

7. The period of incubation in thirteen cases of yellow fever has varied from 41 hours to 5 days and 17 hours.

8. Yellow fever is not conveyed by vomits, and hence disinfection of articles of clothing, bedding and merchandise, supposedly contaminated by contact with those sick of this disease is unnecessary.

9. A house may be said to be infected with yellow fever only, when there are present within its walls contaminated mosquitoes capable of conveying the disease.

10. The spread of yellow fever can be most effectively controled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects.

11. While the mode of propagation of yellow fever has now been definitely determined, the specific cause of this disease remains to be discovered."

Subsequently the U. S. Army Board submitted a report, "*Experimental yellow fever*", by Reed, Carroll and Agramonte, American Medicine, July 6, 1901, in which are described the clinical features of the experimentally produced disease, and in "*the prevention of yellow fever*", by Reed and Carroll, N. Y. Medical Record, October 26, 1901, they describe the *Stegomyia fasciata*, mode of life, habitat, breeding places together with methods for its suppression.

In 1901, during the summer, Dr. Carroll was again detailed to go to Cuba for the purpose of continuing the investigation into the causation and prevention of yellow fever. During this summer Dr. Carroll demonstrated by experiments, that the etiologic agent for yellow fever would pass through a Berkefield Filter, which would prevent the passage of the "Micrococcus aureus". He demonstrated its thermal death point at 55 C., when left at this temperature for ten minutes, although he could find nothing, to which to ascribe the cause itself of the disease. He autopsied a fatal case of experimental yellow fever (A case of Dr. John Guiteras), the first fatal case experimentally produced, and found identical lesions with non-experimental yellow fever.

All of Dr. Carroll's work has been renewed and confirmed by U. S. Marine Hospital Service at Vera Cruz, and by a Commission from the Pasteur Institute working in Brazil („La Fièvre Jaune" by M. M. Marchoux, etc. etc., Annales de l'Institute Pasteur, Nov. 1903) and to-day stands practically as he reported — unadded to and without correction.

Under date of October 26, 1901, Maj. Reed, the head of the Yellow Fever Commission, writes Dr. Carroll concerning that summer's work saying:



"My dear Doctor :

I have just received your letter of the 22nd and hasten to congratulate you on the thorough manner, in which you have accomplished the task assigned you. The results could not have been better, and throw a flood of light on the etiology of yellow fever. We can now go ahead and submit a contribution on the etiology of yellow fever. This we must do promptly after we have discussed all the later results.

Again congratulations. Hoping to see you back soon.

Sincerely yours (W. Reed)."

This they did in an article, "*The etiology of yellow fever, a supplemental note*", (American Medicine, February 22, 1902).

This later piece of work, just like the first most important experiments, all fell upon the shoulders of Carroll. That he well bore that responsibility is best attested by the letter of Reed just cited, which at the same time shows upon whom the real responsibility rested, and gave him credit for the work done. In reporting this work as the first, Maj. Reed, of course, by reason of his superior military rank as Army Surgeon, appears in the Medical literature and Army medical reports, as being the head of the Commission, which technically he was, though, as already pointed out, Carroll was the man really behind the guns, and in actual personal charge during the crucial tests, and at the Carroll Memorial Meeting of the Johns Hopkins Assoc. for Med. history as Professor Wm. H. Welch has repeatedly said to me personally, "*Carroll was the real hero of this memorable commission*".

After the lamented death of Reed, November 1902, Dr. Carroll still continued to take an active part in the study of yellow fever, and in November 1903, he published an article setting forth in detail his work investigating the "*Mixococcidium Stegomyiae*", alleged by Working Party No. 1, Yellow Fever Institute, U. S. Public Health and Marine Hospital Service to be the specific cause of Yellow Fever. This organism Dr. Carroll demonstrated to be a yeast fungus, and not at all related to the causation of yellow fever. He found it present in mosquitoes fed on over-ripe bananas purposely besmeared with yeast culture, but always absent, when mosquitoes were fed on laboratory media as above described. See Journal Amer. Med. Assoc., Nov. 28, 1903, entitled "*The Etiology of Yellow Fever*", "*An Addendum*".

During March 1903, in reply to Dr. Finlay's assertions, that the U. S. A. Commission had not given him proper credit for the mosquito theory in explaining the etiology of yellow fever, Dr. Carroll published an article "*The transmission of yellow fever*" (Journal American Medical Association,

May 23, 1903) in which a very accurate account of the work done by Dr. Finlay and by the Commission is given, and in it Dr. Finlay is given full credit for *advancing the theory of the mosquito as probable causative factor*, but shows the real work and proof to have been done by the Army Commission by more precise and scientific methods.

In commenting upon the work of the U. S. Army Commission, Dr. H. H. Donally, George Washington University, Publ. November 1906, makes the comment: "The value of the work of Maj. Reed, the ranking medical officer of the Commission, has been made so prominent since his death as to appear to eclipse the essential work of his colleagues, Lazear and Carroll, by whom was first actually demonstrated that the "*Stegomyia Fasciata*" is the source of yellow fever infection." Thus it shows that while Reed himself made no effort to take credit due to others, still the very rank, that he held as superior tended to confuse those not intimate with the real work, and by whom done, and in this manner let the work of Carroll be underestimated. Carroll himself knew this, though no public expression of his ever insinuated it. However, his real feelings are gotten at by reading a personal letter to the writer. Carroll and myself were close personal friends, our friendship dating from the time, when Carroll was at the University of Maryland an undergraduate, and later when he was affectionately known as "Jim" Carroll. I had many personal interviews with him and conversations concerning his experiences in Cuba, and, in March 1907, I wrote to my friend informing him, that the degree of Doctor of Laws, *honoris causa*, would be conferred upon him in May 1907, at the One-Hundredth Anniversary of the University of Maryland, in recognition of his valuable contributions to science. The following is, with one omission, a copy of his last letter to me, and I am told the last he ever wrote, and the remark at the end of this letter, "*Great is the Truth, and it will prevail*", had reference to the fact, that Carroll knew, that I was in full possession of all the data of his life work, and it was but a natural expression of gladness, that his fellowmen would realize later on the real worth of his great sacrifice, for he himself had never laid claim to recognition. What had come to him, came by sheer force, and over the barrier of subordinate army rank. His last letter to me was written partially in the recumbent position in bed. I had no knowledge of the gravity of his illness, otherwise I would have visited him in Washington and saved him the labor of letter writing.

This is a copy of his last letter:

Washington, D.C., 1433 Clifton St., N.W., May 27, 1907.

Dear friend Hemmeter :

Of course you will have deemed me ungrateful and inappreciative of the great honor to be conferred upon me by the Old University, my honored *Alma Mater*, but it is not so. I have been sick in bed since February 17th, running a temperature every day, except for three days, when it was temporarily controlled by aspirine. As I write now my temperature is above 100 (2 P.M.) and rising, and I am sitting up contrary to the advice of my physician friends. Nevertheless I have felt all along, that I would send nothing but an autograph reply, and this I have delayed day after day in the hope, that I would soon gain sufficient strength to write a long and satisfactory letter. The visit of my dear friend, Dr. I. S. Stone, enabled me to rest more comfortably afterward, because I felt, that he would explain the circumstances to you. I am sorry to say that during the past four or five days my heart has needed a little coaxing, for all attempts to sit up proved too much, though I felt very well while lying down.

With this explanation, I trust you will pardon my apparent rudeness in thus delaying my response to your communication, that made me very happy indeed. I assure you most sincerely that, apart from personal affliction, it gives me the deepest sorrow to feel, that I am forced to be absent from such a happy and inspiring reunion. As it is, I feel that if I am up and about with a serviceable though damaged heart within 30 days, I shall have cause for further congratulations.

Permit me to express to you as best I can my humble appreciation of the high honor to be bestowed upon me, and to hope that at some future date I may be able to express my gratitude in person.

In one of your letters, you ask for a list of publications, which I enclose. It will give me great pleasure to send you a set of such of the reprints as I have.

You ask me, whether I am infected as the result of our work. Certainly I was. I was the first to propose, that we submit and the first to be infected, though not the first to be bitten.

I am sending by this mail a paper by my friend, Dr. H. H. Donally, and this may be relied upon as accurate in every particular.

There is no foundation for the statement, that Dr. Reed aided me very materially in securing my medical education. As a matter of fact, he had nothing whatever to do with it, and I was never associated with Dr. Reed in any way until I met him at the Army Medical School in Washington late in September 1893. The order for me to proceed there was issued upon recommendation of Surgeon General Sternberg. At this time I had

obtained my medical degree, had taken my post-graduate courses in bacteriology and pathology at the Hopkins (see Register 1891—1892 and 1892—1893) and had put in one summer working independently in the Army Laboratory at the World's Fair in 1893, for which I hold a certificate.

*Great is the Truth and it will prevail!*

Believe me most gratefully,

Fraternally and sincerely yours,

(Signed) James Carroll.

The Degree of Doctor of Laws — "Honoris causa" was conferred on Dr. James Carroll by his Alma Mater during the Centennial Celebration of the University of Maryland May 30th to June 2nd, 1907. As he was very sick at the time, it was the only degree conferred on an American "in absentia".

The University of Iowa also conferred the same honorary degree upon him.

In March 1907, Carroll's military rank was raised from Lieutenant Surgeon to Major in the United States Army, by special Act of Congress. This Act of Congress was undoubtedly prompted by the following recommendation of the National Legislative Council of the American Medical Association, published in the Journal of the American Medical Association, January 20th, 1906:

REPORT ON GOVERNMENT RECOGNITION OF THE SERVICES  
OF DR. JAMES CARROLL.

"Dr. John S. Fulton, of Maryland, introduced the following:

*"Whereas*, In the Year of our Lord Nineteen Hundred, a Yellow Fever Commission was appointed by the Army of the United States to investigate the causes of yellow fever and to devise means for its eradication, the said Yellow Fever Commission consisting of Dr. Walter Reed, surgeon in the Army of the United States, Dr. James Carroll, Dr. Jesse Lazear, and Dr. Aristides Agramonte, acting assistant surgeons in the Army of the United States; and

*"Whereas*, The said Yellow Fever Commission, consisting of Dr. Walter Reed, Dr. James Carroll and Dr. Aristides Agramonte (Dr. Jesse Lazear, deceased), did then and there determine the cause of yellow fever, and devise means for its prevention, by which means yellow fever was eradicated from Havana and Cuba, and thousands of lives have been saved in the United States and other parts of the Western Hemisphere; and

*"Whereas*, Dr. Jesse Lazear, an acting assistant surgeon in the Army of the United States, did subject himself to the bite of an infected mosquito, from which bite Dr. Jesse Lazear suffered death; and



"Whereas, Dr. James Carroll, an assistant surgeon in the Army of the United States, did subject himself to the bite of a mosquito infected with yellow fever, being the first attack ever experimentally produced; be it

"Resolved, That the National Legislative Council of the American Medical Association expresses its appreciation of the valuable work accomplished by the Yellow Fever Commission in the interest of humanity, the material and bodily welfare of the people and of the Army of the United States, and of the heroism and devotion of the aforesaid Major Walter Reed (deceased), Dr. James Carroll, Dr. Aristides Agramonte and Dr. Jesse Lazear (deceased); and be it further

"Resolved, That this Council commend to the Government of the United States adequate recognition of the gallant and meritorious services of the said Dr. James Carroll, the only surviving member in the Army of the United States of the said Yellow Fever Commission."

This report was unanimously adopted by a standing vote.

The following quotation from the British Medical Journal, September 8th, 1906, will serve as an indication of the esteem in which the achievements of the American Yellow Fever Commission are held in England:

"Major Ronald Ross's discovery, that malaria is conveyed by mosquitoes, which act as an intermediate host, has not only led to successful measures to practically eradicate malaria with its attendant evils, but has given the clue to the cause of yellow fever and its treatment, etc. The first positive proof, that the *Stegomyia* was the carrier of the infecting agent of yellow fever, was given, when Carroll, in July 1900, offered himself for a test experiment with a self-sacrifice worthy of all praise. He had a very narrow escape, but Lazear, of the American Commission, and Myers, of Liverpool, lost their lives. That the labors and said deaths of these heroic men were not in vain is amply attested by the remarkable vigour and success, with which the recent plague was stamped out, and the exemption secured by Havana and other pest centers."

In an editorial, the British Medical Journal, Sept. 8, 1906, proposes that the Nobel prize be divided between Dr. James Carroll and Dr. Aristides Agramonte. This at a date, when Carroll was still living:

"In regard to yellow fever, Panama affords as striking an object lesson as Havana of the incalculable benefit to mankind, that had followed the discovery of the cause of the disease and the manner of its transmission. The glory of the work, which has had this striking consummation is shared by several men. The credit of the conception belongs to Dr. Carlos Finlay, who propounded the idea many years ago without attracting from the

profession any attention but an occasional contemptuous notice. More fortunate than many true begetters of new truths, Dr. Finlay, at the meeting of the Pan-American Medical Congress, held at Havana, in 1901, was acclaimed by the assembly as the author of the discovery, which has already been so fruitful of good effects. Dr. Carter was another pioneer in the work, which was brought to completion by the American Commission. Ultimately death snatched the reward from the hands of Walter Reed and Lazear, but Drs. Carroll and Agramonte still survive. It would, we think, be a fitting acknowledgement of the work of these four men, if the Nobel prize were divided among them. It will scarcely be denied by any one conversant with the facts, that their work is of far greater importance than that of several, to whom the prize has been awarded in the past few years. The only original research work, whose practical results can be held to compare with it, is that, which had brought malaria, that monster, which till lately claimed so vast a tribute of human lives, within the control of man."

The following is quoted from the message of the President of the United States to the Senate (59th Congress, Second Session Document No. 10):

"On August 2, 1900, before the mosquitoes were ready for experiment, Dr. Reed was called back to Washington to prepare for publication the abstract of the report of the board, appointed in 1898 to investigate the spread of typhoid fever in the volunteer camps in the United States, of which board he was president.

During Dr. Reed's absence the inoculations by means of the mosquito were begun. On August 11th, Dr. Lazear made the first experiment, but nine distinct inoculations on persons including himself and acting Assistant Surgeon A. S. Pinto were unsuccessful. We know now, that these failures were due to two facts — first, that patients after the third day of the disease cannot convey the infection to the mosquito, and second, that after having bitten a yellow fever case, the mosquito cannot transmit the disease until after an interval of at least twelve days. On August 27th one mosquito was applied to Dr. Carroll, one which happened to fulfil both of these conditions. The result was a very severe attack of yellow fever, in which for a time his life hung in a balance. This was thus the first experimental case. The fever developed on the 31st of August, on which day Dr. Lazear applied the same mosquito, which bit Dr. Carroll with three others to another person. This man came down with a mild but well-marked case.

The second member of the commission was Dr. James Carroll, at that time acting assistant surgeon, United States Army.

Dr. Carroll is now 52 years old. He entered the military service June 9, 1874, and served as private, corporal, sergeant and hospital steward from that date to May 21, 1898, when he was appointed acting assistant surgeon. He was appointed first lieutenant and assistant surgeon in the Medical Corps, October 27, 1902, which rank he still holds.

Dr. Carroll was Dr. Reed's truest assistant and coadjutor from the inception of the work, which resulted in the discovery of the method of propagation of yellow fever. As stated above, the third series of experiments were performed by Dr. Carroll alone, Dr. Reed having been refused permission to return to Cuba to complete his work.

Dr. Carroll was the first experimental case of yellow fever, and he suffered a very severe attack, to which he attributes a heart trouble, from which he now suffers. At the time of undergoing this experiment he was 46 years old, an age from which the risk from this disease is very great, as its mortality rapidly increases with age of patient. He had at that time a wife and five children, who had no other means of support except his pay as an acting assistant surgeon.

It is recommended, that Congress be asked to pass a special act promoting Dr. Carroll, on account of his services in connection with this discovery and the courage shown by him in subjecting himself to experiment, to the rank of lieutenant colonel, the number of medical officers in that grade being increased by one for that purpose; also his name and effigy should appear on the monument to Walter Reed.

Dr. Jesse W. Lazear was the third member of the commission. Dr. Lazear was a native of Baltimore and a graduate of Johns Hopkins University, afterwards getting his professional degree at Columbia University and Bellevue. At the time he incurred his death in the course of these experiments, as above mentioned, he was 34 years old. He left a wife and two young children, the younger a little son born a few months before his death, whom he never saw. Mrs. Lazear received from Congress a pension of \$17 a month with \$2 additional for each of two minor children, until they reach the age of 16. Also a battery in Baltimore harbor was, by direction of the Secretary of War, named in his honor. It is believed that this recognition on the part of the nation for his services is utterly inadequate. His widow's pension should be increased to \$100 per month, and steps should be taken to perpetuate his name in connection with the Walter Reed monument above suggested.

Dr. A. Agramonte was the fourth member of the yellow fever commission. He was a Cuban by birth, an immune to yellow fever, and having been assigned other work, took no part in the first series of experiments with regard to the conveyance of the disease by the mosquito, of which,

in fact, he was not at the time cognizant. Being an immune he ran no risk in connection with this work, and it is believed, that his contributions to it have been sufficiently recognized in the association of his name with the other members of the commission, who brought about this great discovery.

Twenty-three of the men, who submitted themselves for experiment by the board, contracted yellow fever, beginning with Dr. James Carroll, who was taken sick August 31st, 1900, and ending with John R. Bullard, who was taken sick October 23, 1901.

Conspicuous among them was John J. Moran, a civilian clerk, employed at the headquarters of General Fitzhugh Lee, at Quemados, who was one of the earliest volunteers for the second set of experiments, and whose action was dictated by the purest motives of altruism and self-devotion. Mr. Moran disclaimed, before submitting to the experiments, any desire for reward, and has never accepted any since, although he was offered the \$200, which the liberality of the military governor enabled the commission to give to each experimental patient, the members of the board excepted. Such was his modesty, that he has made no effort, so far as known to this office, to make known his connection with these experiments and reap the credit, which is so justly due him. Mr. Moran was a native of Ohio. His present address is not known to this office. The first inoculations in the case of Mr. Moran were for some reason, unsuccessful, on November 26th and 29th. He did not suffer an attack until after the third inoculation on December 21st.

The same remarks apply to the first experimental case of the second set, Private John R. Kissinger, Hospital Corps, who volunteered at the same time with Moran and equally disclaimed any desire for reward.

Private Kissinger did not leave Cuba immediately after the experiments, as did Mr. Moran, and therefore the military authorities were able to reward him in some measure along with the other enlisted men, who volunteered for these experiments. He was promoted acting hospital steward, presented with a gold watch by the chief surgeon of the department in the presence of all the medical officers and hospital corps men on duty at the Columbia Barracks, and also received a present of \$150 in cash. He took his discharge November 14, 1901, and has since (on December 19, 1903) made application for pension. This was refused for lack of evidence, that his ill-health was incident to the service.

Of the other experimental cases, seven were Spanish immigrants, who submitted to experiments purely for the money, which they were promised. With regard to those, who were American soldiers, however, ten in number, in addition to those already mentioned, it cannot be doubted that, although



they received pecuniary rewards, a desire to assist in what they appreciated was a great and glorious work, together with a spirit of adventure, was the most powerful motive. The same is true of the last experimental case, Mr. John R. Bullard, a graduate of Harvard, where he was a distinguished athlete and captain of the University crew. The names of these men, with the dates of their attack, is appended with this report."

Names of persons, who submitted to experimental inoculation of yellow fever,  
Cuba, 1900—1901.

<i>Infected by mosquitoes.</i>	<i>Taken sick.</i>
1. James Carroll . . . . .	Aug. 31, 1900
2. X.Y. (American soldier) . . . . .	Sept. 6, 1900
3. John R. Kissinger . . . . .	Dec. 8, 1900
4. Nicanor Fernandez . . . . .	Dec. 13, 1900
5. Antonio Benigno . . . . .	Dec. 13, 1900
6. Becente Presedo . . . . .	Dec. 15, 1900
7. John J. Moran. . . . .	Dec. 25, 1900
8. Jose Martinez . . . . .	Jan. 3, 1901
9. Levi E. Folk . . . . .	Jan. 23, 1901
10. Clyde L. West. . . . .	Feb. 3, 1901
11. James L. Hanberry . . . . .	Feb. 9, 1901
12. Charles G. Sonntag . . . . .	Feb. 10, 1901
13. Pablo Ruiz Castillo . . . . .	Sept. 19, 1901
14. Jacinto Mendez Alvarez . . . . .	Oct. 13, 1901

<i>Infected by injection of blood.</i>	
1. Warren G. Jernegen. . . . .	Jan. 8, 1901
2. William Olson . . . . .	Jan. 11, 1901
3. Wallace Forbes . . . . .	Jan. 24, 1901
4. John H. Andrus . . . . .	Jan. 28, 1901
5. Manuel Gutierrez Moran . . . . .	Oct. 20, 1901
6. John R. Bullard . . . . .	Oct. 23, 1901

<i>Infected by injections of filtered blood serum.</i>	
1. P. Hamann, Twenty-third Battery Coast Artillery. .	Oct. 19, 1901
2. A. W. Covington, Twenty-third Battery Coast Artillery	Oct. 19, 1901

<i>Exposed to Fomites.</i>	
1. Dr. R. P. Cooke, acting assistant surgeon.	
2. Levi E. Folk.	
3. Warren G. Jernegan.	
4. James L. Hanberry.	

5. Edward Wealherwalks (bitten once, negative; refused after Hanberry came down).
6. James Hildebrand (offered himself, but was declined on account of age).
7. Thomas M. England.

Major James Carroll died on the 16th of September 1907, in Washington. He had informed me on several occasions, that he had not been a sound man since that memorable experimental infection in August 1900, which should constitute one of the most important discoveries in the history of medicine. But his interest in the subject of yellow fever did not cease with the discovery of the method of its transmission, for he continued to make many later contributions to this important subject, as the appended list of his publications will indicate. He was buried with military honors usually accorded to a major of the United States Army. Scientific and military men of the highest rank considered it an honor to act as pall bearers and escorts at this funeral.

The U. S. A. yellow fever commission has through the talents of Reed, Carroll, and Lazear, contributed to humanity and to their country a service, the value of which cannot be overestimated. This discovery was made possible through the heroism of James Carroll. The United States has been invaded by yellow fever 90 times, carrying death and destruction into New Orleans, New York, Philadelphia, Memphis, Baltimore, Charleston, Galveston, Portsmouth, and many smaller cities. In 1793 it wiped out 10% of Philadelphia's population, and the epidemic of 1853 cost New Orleans 8000 lives. In the message from the president of the U. S. to the senate (59th congress, second session, document no. 10) dated Dec. 5th 1906, it is stated, page 7, by surgeon general U. S. A. R. M. O'Reilly, that the total disbursements of this great nation in the way of rewards for those, who made possible this brilliant discovery amount to \$146 a month. Since Carroll's death this has been increased by \$25 a month, the pension of a widow of a major U. S. A. Prof. William H. Welch, of the Johns Hopkins University, who was the distinguished teacher of Major Carroll, in the same message, calls attention in a letter to the secretary of war to the saving of thousands of lives through this discovery, which would have been impossible without Carroll's great sacrifice.

The English Government voted Sir William Jenner, the discoverer of vaccination, various grants amounting to 30,000 pounds sterling. India presented him with a subscription of 7,323 pounds. It is important to call the attention of the committee on pensions in the senate and congress to these liberal grants, for we believe, that it is the wish of the American people to emulate them, lest the old accusation about the ingratitude of

republics shall again come true. The widow of Dr. Jesse Lazear, the third member of the yellow fever commission, receives a pension of \$ 17 a month, with an additional \$ 2 for each of the two minor children until they reach the age of 16. The pension of the widow of Dr. Lazear, as well as of the widow of Major James Carroll, should be increased to \$ 125 a month.

There is however one very important and essential desideratum, which I consider it my duty to emphasize in this connection, and that is, that the life and work of Major James Carroll, as well as Dr. Jesse Lazear, should be represented in a monument with a prominence equal to that given to Major Walter Reed; for there can be no just distinctions made between the merits of these three benefactors, and any comparisons aiming to bring out personal preferences would be decidedly invidious. Applicable to the life and work of all three is the beautiful sentiment of Horace,

*"Integer vitæ scelerisque purus"*

and there rarely has been an incident in the history of medicine, in which the lives of three distinguished men were directly or indirectly sacrificed for one great purpose — thereby securing to each one of them a place in the *Walkhalla* of American History.

#### H O R A C E ' S M O N U M E N T .

I've reared a monument — my own —  
More durable than brass;  
Yea, kingly pyramids of stone  
In height it doth surpass.

Rain shall not sap, nor driving blast  
Disturb its settled base,  
Nor countless ages rolling past  
Its symmetry deface.

I shall not wholly die. Some part,  
Nor that a little, shall  
Escape the dark Destroyers' dart,  
And his grim festival.

As long as, with his Vestals mute,  
Rome's Pontifex shall climb  
The Capitol, my fame shall shoot  
Fresh buds through future time.

Where brawls loud Aufidus and came  
 Parched Daunus erst, a horde  
 Of mystic boors to sway, my name  
 Shall be a household word.

As one, who rose from mean estate,  
 And first, with poet's fire,  
 Aeolic song to modulate  
 To the Italian lyre.

Then grant, Melpomene, thy son  
 Thy guerdon proud to wear,  
 And Delphic laurels, duly won,  
 Bind thou upon my hair.

Inscription on Bronze Memorial Tablet to be erected in the Medical Building of the University of Maryland in honor of *James Carroll*, Major and Surgeon U. S. Army. M.D. (1891) and LL.D. (1907) University of Maryland LL.D. (1907) University of Nebraska, Professor of pathology and bacteriology, Columbian Univ. Wash. D.C. Born in Woolwich, England June 5th 1856. Died in Washington D.C. September 16th 1907.

As a member of the army commission, which succeeded in demonstrating the mode of conveyance of yellow fever, he became an eminent contributor to science by his investigations and a heroic benefactor of his country and of mankind by voluntary submission to the bite of an infected mosquito, whereby he suffered from a severe attack of yellow fever, produced for the first time by experiment.

"Greater love hath no man shown than this, that a man lay down his life for his friends."



*List of Dr. Carroll's independent contributions to the literature of yellow fever.*

- "The Treatment of Yellow Fever", Jour. Amer. Med. Assoc. July 19, 1902.  
 "The Transmission of Yellow Fever", Jour. Amer. Med. Assoc. May 23, 1903.  
 "The Etiology of Yellow Fever an Addendum", Jour. Amer. Med. Assoc.  
 Nov. 28, 1902.  
 "Remarks on the History, Cause, and Mode of Transmission of Yellow  
 Fever, etc." Jour. Assoc. Military Surgeons, 1903.  
 "A Brief Review of the Etiology of Yellow Fever", N. Y. Med. Journ.  
 and Phil. Med. Jour. (consol) Feb. 6 and 13, 1904.  
 "Without Mosquitoes There Can Be No Yellow Fever", Amer. Medicine,  
 March 17, 1906.

*Contributions of Dr. James Carroll together with Dr. Walter Reed.*

- 1899 a. Bacillus icteroides and Bacillus cholerae suis. A preliminary note.  
 Med. News, N. Y., v. 74 (17) Apr. 29, pp. 513—514.  
 1899 b. The specific cause of yellow fever. A reply to Dr. G. Sanarelli.  
 Med. News, N. Y., v. 75 (11), Sept. 9, pp. 321—329.  
 1900. A comparative study of the biological characters and pathogenesis  
 of Bacillus x (Sternberg), Bacillus Icteroides (Sanarelli), and the  
 hog-cholera bacillus (Salmon and Smith). (Received for publication  
 Feb. 25.) J. Exper. M. (Balt), v. 5 (3), Dec. 15, pp. 215—270,  
 figs a—o, pl. 19, figs 1—3.  
 1901. The Prevention of yellow fever. (Read at 29th Ann. Meeting, Am.  
 Pub. Health Ass., Buffalo, Sept. 16—21.) Med. Rec., N. Y. (1616),  
 v. 60 (17), Oct. 26, pp. 621—649, figs 1—10.  
 1902. The etiology of yellow fever. A supplemental note. (Read at 3d  
 Ann. Meeting, Soc. Am. Bacteriologists, Chicago, Dec. 31, 1901  
 and Jan. 1, 1902.) Am. Med. Phila., v. 3 (8), Feb. 22, pp. 301—305,  
 charts 1—6.

*Publications of Dr. James Carroll together with Dr. Walter Reed  
 and Dr. Aristides Agrimonte.*

- 1901 a. The etiology of yellow fever. An additional note. (Read at Pan-  
 Amer. Med. Cong., Havana, Cuba, Feb. 4—7.) J. A. Med. Ass.  
 Chicago, v. 36 (7), Feb. 16, pp. 431—440, charts 1—6.  
 1901 b. Experimental yellow fever. Am. Med. Phila., v. 2 (1), July 6,  
 pp. 15—23, charts 1—8, tables 1—2.

*Publications of Dr. James Carroll together with Dr. Walter Reed,  
 Dr. Aristides Agrimonte and Dr. Jesse W. Lazear.*

1900. The etiology of yellow fever. A preliminary note. (Read at meeting  
 of Am. Pub. Health Ass., Indianapolis, Ind., Oct. 22—26.) Phila.  
 M. J. (148) v. 5 (17), Oct. 27, pp. 790—796, tables 1—3, charts 1—2.

Headquarters of the Army,  
Adjutant Generals Office,  
Washington, May 24, 1900.

Special Orders No. 22.

Extract.

× × × × × × × × ×

33. By direction of the Secretary of War, Major Walter Reed, surgeon U. S. Army, and Acting Assistant Surgeon James Carroll, U. S. Army, upon completion of the duty assigned them by the Commanding General, Department of the East, will proceed to Camp Columbia, Quemados, Cuba, on official business pertaining to the Medical Department, and report their arrival and instructions to the Commanding General, Division of Cuba; the Commanding General Department of Havana and Pinar Del Rio and the Commanding Officer, Camp Columbia. The travel enjoined is necessary for the public service.

34. By direction of the Secretary of War a Board of Medical Officers is appointed to meet at Camp Columbia, Quemados, Cuba for the purpose of pursuing scientific investigations with reference to the infectious diseases prevalent on the Island of Cuba.

Detail for the Board:

Major Walter Reed, Surgeon, U. S. Army.

Acting Assistant Surgeon, James Carroll, U. S. Army.

Acting Assistant Surgeon Jesse W. Lazear, U. S. Army.

The Board will act under general instructions to be communicated to Major Reed by the Surgeon General of the Army.

By command of Major General Miles

H. C. Corbin,

Adjutant General.

A true copy.

Camp Columbia, Quemados, Cuba.

July 16, 1900.

My Dear Jamie:

Your letter of July 11, came with Mamas letter this morning. It was very nicely written and I was glad to receive it. I am glad if David has learned to ride so soon but I hardly think he could have done so in a few minutes. Can he mount from the pedal? Can he dismount without falling and can he turn a corner without running into somebody. I think Papa will have to see David ride for himself, because you try to fool your poor old Pop sometimes.

Now about your coming down here with David and Tracy. If you fellows come, you will probably have to stay until the new year and while you are down here, I will have to pay \$ 1 a day for board for each of you and \$ 2 or \$ 3 a month for washing, which would amount to about \$ 65 a month. Now if Mama will agree for me to pay that out of her \$ 100 all right and then she can pay your fare to New York and hotel bill and carfare and transfer etc. And then there is yellow fever in this country; they call it "Yellow Jack" because people, who have it, turn yellow after they die. And when they are sick they give them nothing to eat sometimes for a week, and I think you would not like that.

And then what would Mama do, without you boys to look after her, while Papa is away? And you would have to miss your school and music lessons too. Papa wants you to learn all you can, while you are young, because if you do not, when you grow up, you will not be able to do great work or command large salary. Everything you learn now, my boy, will make your life easier for you, when you become a man. Learn to spell above all things; then study grammar and learn how to speak and write, and study history and geography to know about people and countries. You ought to learn something now about China because the Chinks have murdered a lot of white people, men, women and children and there will be a big war over there soon.

Good night my dear boy, and with love and kisses from your loving  
Papa.

Camp Columbia, Quemados, Cuba.  
July 24, 1900.

My Dear Jennie:

Your letters written on the 18th and 19th telling me about the baby's illness came yesterday and I have felt very miserable since. If her teeth are the cause of the suffering, I am surprised, that you did not scratch her gums yourself with the point of a knife soaked in carbolic acid and then rinsed in boiled water. You know it sometimes gives relief and does no harm. A few drops of nitre in water for her fever and to sleep at night in the room downstairs with the doors and windows open and frequent sponging is about all, that one can do. If she is weak a few drops of good sherry in boiled water and sweetened ought to hold her up. It is the usual attack, that all babies must go through and with care I hope she will be all right. But I shall be dreadfully worried, until I hear from you, and indeed until I learn, that she is better as I earnestly hope she will be or is by this time.

Yesterday, as the mail came in, I was about to leave for the camp at





the Surgeon General, who, of course will inform you at once. I did not cable to you, for I feared, that you might not be at the Museum, and that the news might get to Mrs. Carroll in an improper form.

He had a headache on Friday August 31, and in the evening I found his temperature to be 102. Next morning, however the temperature was 98.4 and we thought all was well. I could find no malarial parasites. Later in the day the temperature gradually mounted to 103.8, the pulse falling from 90 to 80. This morning temperature is still high 103.5 and there is a good trace of albumin in the urine. Headache and photophobia are marked. He took two good purges on the 31st and on Sept. 1st. He was taken to the isolation camp this morning. He seems much worried, but is not restless at present. It was hard to keep him in bed at first. I shall keep you informed. Dr. Gorgas was out this morning and I shall ask him to come frequently.

Most sincerely,

Jesse W. Lazear.

Camp Columbia, Quemados, Cuba.

Sept. 3, 1900.

My Dear Mother:

I have a very light case. No cause for alarm. A change this evening for the better. Will keep you posted by every mail.

Yours,

James.

(This was written by his nurse Mrs. Lena Wamer).

September 7, 1900.

1:15 p.m.

My Dear Carroll:

Hip Hip Hurrah; God be praised for the news from Cuba today — "Carroll much improved — Prognosis very good." × × × × Really I can never recall such a sense of relief in all my life as the news of your recovery gives me.

× × × × × × ×

Reed.

War Department,

Surgeon General's Office,

Army Medical Museum and Laboratory,

Washington, Sept. 7, 1900.

My Dear Doctor Carroll:

I cannot begin to tell you, how delighted I was to hear, through cable from Dr. Kean, that you are better. Thank Heaven for that much. Do

pray keep up your courage and pull through. It is not necessary for me to tell you, that I have been utterly wretched and unhappy over the news of your sickness. Your many friends in Washington are so very anxious about you. When I told Hagner this morning, that you were better, he clapped his hands through the telephone and said "Oh Doctor Reed I never was so glad to hear anything in my life". Mrs. Carroll though shocked bears the news like the brave woman, that she is. Your children are all well, but know nothing of your sickness. Again, thank God for your improvement. Keep up the good work. Love to Doctores Ames and Dear Lazear, who have so nobly cared for you.

Affectionately,

Reed.

Camp Columbia, Quemados, Cuba.

Thursday afternoon, Sept. 13, 1900.

My Dear Jennie:

It seems impossible, that I have been sick in bed two weeks, and that I have been so nearly passing in my checks. This is my first attempt at writing and I am still very weak indeed, so weak that I cannot attempt stand or change my position without assistance. But I have been disinfected and have been taken back into my old quarters again, I look like a scarecrow, I have lost much in weight, my beard is long and I am thoroughly worn out. I shall pull up rapidly again. A steady life has saved me

× × × × feel too tired to write much more today.

Your affectionate husband,

James.

Camp Columbia, Quemados, Cuba.

Tuesday Sept. 18, 1900.

My Dear Jennie:

I write to let you know, that I am picking up as rapidly as a person could, gaining every day. I heard to day, that the Surgeon General leaves Washington for about two weeks, and that Doctor Reed will probably start in a day or two for here. It would do you good to see me eat at every meal and I am growing stronger and stronger every day. I weighed this morning and tipped the scales at 152-1/2 pounds, which is only seven pounds lighter than before I was taken sick.

× × × × × × ×

Another case has come down here, since I have been reported convalescent. He is Major Cartwright the chief quartermaster of the Department. He is 38 years of age and has a temperature running about the

same as mine. He is probably not so strong as I was and at this stage no one can tell, what the result will be. One thing is certain Jennie, I am now entirely free from danger and incapable of contracting the disease.

× × × × × × ×

Do not worry about me now Jennie. I am perfectly safe and it is only a matter of a short time, when I will be back with you.

Your affectionate husband,  
James.

Blue Ridge Summit, Pa.  
Sept. 19, 1900.

My Dear Carroll:

A letter from Dr. Lazear dated Sept. 13 said, you were to return to quarters on that day and that you were rapidly picking up strength. I am so delighted to know, that you are once more yourself. Have you decided whether you will return to the United States on leave of absence or not? In conversation with Mrs. Carroll prior to your attack of yellow fever she said, that if you have to return to Cuba, she would rather that you stay until Xmas and then come home for good. In other words she did not like the idea of your returning after you once got home. I shall come down about the first of October and perhaps may still find you at Columbia Barracks. I hope to see you wether there or in Washington, before I sail. I think that we can all get back home by December 20th. That is my present expectation. How does it feel to be an immune?

Sincerely yours,  
Walter Reed.

Camp Columbia, Quemados, Cuba.  
Sunday, Sept. 23, 1900.

My Dear Jennie:

I write this to let you know, that I am still alive and gaining strength. I look forward to morrows mail for some news from Doctor Reed as I have not heard a word from him and do not know, what to expect. Agramonte left for New York yesterday with his wife and Doctor Lazear is still very ill with about even chances for his recovery. Major Cartwright, who was the next to take yellow fever after me, died this morning. I asked for an autopsy and it was refused. Doctor John Guiteras, formerly Professor of Pathology at the University of Pa. called to see me this afternoon as also did Dr. Gorgas and Dr. Finley. Everybody is surprised

at the manner in which I am picking up flesh ad strength and all these yellow fever experts remarked how strong I was upon my legs. Yellow fever has no terrors for me now, because I am an immune and cannot contract it again, which gives me a great feeling of comfort.

× × × × × × × ×

Your affectionate husband,

James.

Camp Columbia, Quemados, Cuba.

September 28, 1900.

My Dear Jennie:

I received no letter from you by the last mail, so I have none to answer. I inclose one, that I received from Dr. Reed this morning so that you can see the suggestion for me to remain down here until the end of the year; I have written to him just as I feel, that I have put on flesh rapidly, but I am very weak; yet I think that the sea trip and short visit to the United States will build me up greatly. I am sick of this Cuban diet and long for some American oysters and fruits. If it is only for 10 days I can come back stronger and better able to work.

Dr. Lazear died tonight after a week's illness. He was taken sick just a week ago this evening 8:00 o'clock and died tonight at about the same time, so I suppose, that I may regard myself as a lucky individual.

As you will see from Dr. Reed's letter he expects to start October 1, and will reach here about the 5th. I shall try and get back as soon as possible after he reaches here.

Your affectionate husband,

James.

Camp Columbia, Quemados, Cuba.

Saturday, Sept. 29, 1900.

My Dear Jennie:

× × × × × × × ×

Doctor Reed is coming down again. I received three letters from him today and he tells me, he expects to sail from New York on the 28th and to arrive at Cuba on Wednesday next × × × ×

Kean asked me to have everything in the laboratory disinfected, so it would be safe for Dr. Reed to come and work in.

× × × × × × × ×

A mosquito nearly killed me and another killed poor Lazear; the same



one, that bit me, was allowed to bite another man and he had a mild attack of yellow fever. This is the most important part of our work and Dr. Zeed tells me, that we must publish a small paper about it. Do not mention this to any one for anything just yet, because it is to be kept a profound secret. It is one of the discoveries of the century.

× × × × × × × ×

Your affectionate husband,  
James.

Camp Columbia, Quemados, Cuba.  
Thursday, Sept. 28, 1900.

My Dear Jennie:

There is not anything of special interest to mention today. I have spent about half the day sitting on the porch and the other half looking over Lazear's papers for notes pertaining to our work. There was quite a notice in this mornings papers about Dr. Lazear, and your husband is mentioned too. I mail you the paper × × × × By the way that paper says, that I still have yellow fever. That is not so; I am entirely well and nearly as strong as ever. I can go, where I please and I attended dear Lazear's funeral yesterday. Last Sunday I performed an autopsy, though I was really too weak to undertake it. But the case was really an interesting one and if I had not done it, we would have lost a great deal.

Your affectionate husband,  
James.

Post Hospital, Cuba.  
November 20, 1900.

My Dear Jennie:

× × × × × × × ×

I made my first trip to the City Hospital today, where I was greeted very nicely by some of the Spanish physicians, one of whom patted me approvingly on the back. The cases of yellow fever appear to be very mild, so much so that our work may be interfered with. I applied two mosquitos with a view to having them bite volunteers for further experiments. I have gotten entirely over my attack of cold or grippe, whichever it may have been, and feel perfectly well again.

× × × × × × × ×

Your affectionate husband,  
James.

Camp Columbia, Cuba.  
Thursday, Nov. 22, 1900.

My Dear Jennie:

I received your letters of the 15th and 17th yesterday.

× × × × × × × ×

We have just returned from Havana, where Drs. Reed, Agramonte and myself have been to see the Spanish Consul and General Wood's chief officer. One of the Spanish papers has taken up the matter of our experiments and accuses us of horrible cruelty in enticing Spanish emigrants out to camp by hiring them as laborers, then locking them up in a room at night and turning in a lot of infected mosquitoes to give them yellow fever, without their knowing anything about it. As a matter of fact we do take Spaniards and give them \$ 1.00 a day and board and we offer them a reward to be bitten, if they choose. No compulsion whatever is to be used, and we have American volunteers for the same work, who will be bitten and treated exactly as they are. The Consul says, that so long as the men are of age and consent fully, it is nobody's business. So we will go ahead. Do not speak of this to any one, because we do not want it spread any more than is necessary, until after we have finished.

× × × × × × × ×

Your affectionate husband,  
James.

Camp Columbia, Cuba.  
Sunday, November 25, 1900.

My Dear Jennie:

I received two letters from you yesterday one dated the 18th and the other the 20th.

× × × × × × × ×

I have just returned from paying a happy call with Doctor Reed. We called on Mrs. Dr. Kean, who gave the card party with Mrs. Stark. Captain Slocum, who was on General Lee's staff, was very nice, and he is a neighbor to General Kean's and I was out on the porch with them. He addressed me as "Carroll" and sat with his arm resting on the back of the bench beside me. These people here are all intensely interested in the yellow fever and mosquito question and all are awaiting the result of our experiments.

× × × × × × × ×

A very bitter paper has recently been published against us, so that we

must repeat our experiments, before we can go any further, because many are trying to raise a laugh at our expense.

× × × × × × × ×

Your affectionate husband,  
James.

Cuba, Columbia Barracks, Nov. 25, 1900.

My Dear Jennie:

I send you the Havana Post for yesterday and today. One states that we are creating a sensation in Havana; the other that a party of Cleveland physicians are coming down to attend the meeting of the Medical Congress in Havana next month.

× × × × × × × ×

We drove out to visit Santa Clara Battery, where the captain of the Battery, to which Dr. Reeds son belongs, is stationed. He wanted to call on him and incidentally we wanted to look for mosquitoes. We found some breeding in the captains kitchen, and spent a pleasant afternoon.

× × × × × × × ×

Your affectionate husband,  
James.

The description of a "serum boil" (abscess) in this letter and of an attack of "Grippe" in a previous letter suggests, that Carroll was in feeble health even at this date Dec. 11, 1900 and several months after his so called recovery from yellow fever. J. C. H.

Camp Columbia, Cuba.

Tuesday, December 11, 1900.

My Dear Jennie:

In a conversation with Dr. Reed he stated, that he thought we would probably return to Washington about the middle or the end of February. He is very much elated, because we have obtained a true case of yellow fever from the bite of an experimental mosquito and this confirms our former results. The idea is to read another paper before the Pan American Congress, which meets in Havana this winter. The time of meeting has been postponed from December 26 to February 5, so it will be necessary to wait here until then. He acknowledges the great importance of our work and said, it should entitle us to membership in any of the European Medical Societies. In addition the U. S. Gov't should award a sum of money for the work, but that is all speculation. I had him lance a serum boil for me tonight, and I think my neuralgia will be better in the morning. We have several more men, whom we expect to come down from the bite of a mosquito and a great deal more of this work to do

before the report can be prepared. Th's is the great chance of my life time — it is a perfectly sure thing and some benefit must certainly follow.

This should be our consolation for spending a lonely Xmas and a year hence I hope our position will be much better than now. With love and kisses to the boys, Mabel and yourself.

Your affectionate husband,  
James.

Columbia Barracks, Cuba.  
Saturday, December 15, 1900.

My Dear Jennie:

Your letters of the 8th and 11th of December came today

× × × × × × × ×

I do not think it wise for you to go to any one now, because if they had the disposition to have done something, it could have been done long before now. Now that I have risked my life and earned recognition and fame by my own efforts, I prefer to trust to the friend, who assured me, he would look after my interest and who has never failed me × ×

Your affectionate husband,  
James.

An expression of hope of military advancement and recognition by the U. S. Government.

Columbia Barracks, Cuba.  
Monday, December 17, 1900.

My Dear Jennie:

Tracy was foolish not to have accepted Dr. Reed's offer of \$200. We have had four men bitten since and all have recovered after mild attacks of yellow fever. Tracy did not see Dr. Lazear get the bite, that killed him, though he did see him take one bite. Lazear only permitted an insect, that had been applied to a very mild case to bite him. And nothing followed that bite. The insect, that he applied to me, however, had bitten four cases, all of them *very severe* cases. My attack was a severe one also. The bite, that killed Lazear, was from an insect flying about the hospital ward, one that he knew nothing about, and from which he expected nothing. The result you know.

× × × × × × × ×

Your affectionate husband,  
James.



Columbia Barracks, Cuba.  
Xmas Evening 1900.

My Dear Jennie:

I received your letter of the 20th yesterday × × × × ×  
× × × We have had another case of yellow fever come down  
today. The poor fellow is quite sick. He is a white man, who volunteered  
and is to receive \$ 200. We simply turned some mosquitoes, that had  
bitten another yellow fever patient two weeks before into a house and  
then watched the mosquitoes bite him from another portion of the room,  
which was partitioned off with wire gauze. After 4 days he has come  
down and out of 5 persons, that we have bitten, every one has come  
down at last. This means complete success for us and confusion for  
Sanarelli. Our other paper has been published in the Journal of  
Experimental Medicine and we have 250 reprints in Washington.

× × × × × × × ×

Your affectionate husband,  
James.

Columbia Barracks, Cuba.  
Monday, December 30, 1900.

My Dear Jennie:

× × × × × × × ×

I went to the city yesterday and drew \$ 950 from the bank to pay  
the men, upon whom we have experimented. Out of that I paid \$ 129.00  
for a watch chain and charm to be presented to one of these men for  
his courage in submitting to the inoculation.

× × × × × × × ×

Your affectionate husband,  
James.

Columbia Barracks, Cuba.  
January 23, 1901.

My Dear Jennie:

× × × × × × × ×

We had another case come down today from the bite of a mosquito.  
We are now able to produce cases of yellow fever to order.

× × × × × × × ×

Your affectionate husband,  
James.

Columbia Barracks, Cuba.

Thursday, January 31, 1901.

My Dear Jennie:

× × × × × × × ×

A yellow fever editorial in the Post was very sarcastic and I had lots of fun teasing Dr. Reed about it. × × × × × × × ×

Our paper will probably be ready next Monday, and then watch the American papers. Tell the folks at home to do the same, especially the New York papers, for it will attract some attention. I will send you the Havana papers, so that you can read for yourself, what they say here. We have spent a busy afternoon. The delegates to the Pan American Congress have begun to arrive and this afternoon we entertained the delegates from Mexico, who were very anxious to know something of our work. They have a great deal of yellow fever at Vera Cruz and their Government is anxious to stamp it out. One of the gentlemen is physician to President Diaz; one is an eminent bacteriologist; one has seen more yellow fever cases perhaps than any other man in the world, and another is a military surgeon of high rank. The latter compliments me by saying I was a hero and all were delighted, with what they saw. I send you the Havana Post of today, which contains some allusions to our Commission.

× × × × × × × ×

Your affectionate husband,

James.

Columbia Barracks, Cuba.

February 5, 1901.

My Dear Jennie:

I received your first letter this evening upon my return to the city, where I have been all day listening to the discussion at the Congress. Our paper appears to have been the event of the session and of course my friend received the greatest praise. One of the Cuban physicians raised the point, that it was wrong to experiment with human beings; to this Reed stated in reply, that the first person to come down was a member of the commission — myself. That brought down the house, such as it was.

After the morning session Dr. Agramonte took Dr. Reed and myself to his house for lunch, and it was a lunch. We began with green peas, then radishes, Burgundy wine, then fish, after that fricasseed chicken, then roast beef, with these came Spanisch claret, baked plantains, both green and ripe; next came Neufchatel cheese with orange preserve and this was followed by delicious pine apple and another very rich fruit,

that I had not tasted before, the sabidillo; cigars and coffee finished a very elegant meal; the table appointments were elegant and very fine even to finger bowls.

× × × × × × ×

Your affectionate husband,  
James.

Columbia Barracks, Cuba.  
Sunday February 10, 1901.

My Dear Jennie:

× × × × × × ×

We have just brought down two more cases from mosquito bites and it is well, that I remained here to take notes and observe them. One of them looks as if it might be severe, but I hope he will recover. So far we have not lost a case.

× × × × × × ×

In regard to the Medical Congress, our paper was the only one, that attracted general attention and our work is regarded as being of the greatest importance.

× × × × × × ×

Your affectionate husband,  
James.

Camp Columbia, Cuba.  
February 14, 1901.

My Dear Jennie:

× × × × × × ×

I believe, that I have found the parasite, but I have thought so a number of times before, so I am going slow now. I am examining a number of mosquitoes to be certain, before I make any assertions. Do not mention it to any one.

× × × × × × ×

Your affectionate husband,  
James.

Columbia Barracks, Cuba.  
February 21, 1901.

My Dear Jennie:

× × × × × × ×

I have seen something today, that leads me to believe, I am on the

track of the parasite. But time will be required to determine and I must examine many insects before coming to any decision.

× × × × × × × ×

Your affectionate husband,

James.

War Department

Surgeon General's Office,

Army Medical Museum Library,

Washington, Feb. 26 1901.

My Dear Doctor:

I have yours of the 21st and am afraid this will not reach you in time before your departure. I want you to bring the reprints of our preliminary note, which I seem to have left behind unintentionally. There were about a dozen of them. Be sure and get from Dr. Ames the map, showing the Quamados epidemic, which he was kindly preparing for me. I want it very much and he must have completed it by this time.

× × × × We must present the clinical side of these cases to the Association of American Physicians in May if possible. × × × × I am tied down to the Army Examining Board. × × × × You made no mistake by remaining in Cuba until March as February has simply been atrocious. × × × ×

Sincerely yours,

Reed.

Las Animas, Havana, Cuba.

Sept. 12, 1901.

My Dear Jennie:

× × × × × × × ×

I am looked upon as a bogey man down here but the mosquito is mightier than the shot gun.

× × × × × × × ×

Columbian University,

Washington, D.C.,

Office of the President.

May 24, 1904.

Dr. James Carroll,

Washington, D.C.

Dear Doctor:

It gives me pleasure to inform you, that at a meeting of the Executive Committee yesterday, you were appointed Professor of Pathology and



Bacteriology in the Department of Medicine and also to be in charge of the Clinical Laboratory in the Hospital, and Dr. H. H. Donnelly was appointed to assist you in the latter position.

These appointments were made for the academic year 1904—5. Your compensation will hereafter be fixed.

Very truly yours  
Charles W. Needham.

The New Willard, Washington.  
April 21 (or 28) 1907.

Doctor Edward O. Jordan,  
Department of Bacteriology,  
University of Chicago.  
Chicago, Illinois.

Dear Doctor Jordan:

I owe you a letter of thanks for the kind letter of congratulation received from you several weeks ago, and assure you of my sincere appreciation.

I am unable to look the letter up this evening as I have been on my back in bed for 8 weeks, and this is the first day of the 9th week following an attack resembling influenza, and which is accompanied by an *endocarditis*.

As the endocarditis existed three years ago, it is difficult to say, what role it plays in my present illness, but at any rate I have had a continuous fever, with a temperature at first intermittent and now remittent.

Fortunately the infection appears to be somewhat mild, although very persistent, and I am holding my own very well.

Blood cultures have been made on two occasions each time with negative results. Agglutination tests have been negative. The blood shows no leucocytosis and the counts are practically normal. This of course excluded the ordinary pus organisms and I still cling to the possibility, that the infection may have been set up by the bacillus of Pfeiffer.

I have written to Doctor Ford of the Johns Hopkins, Doctor Ernst of Harvard and Doctor Winslow of the Massachusetts Institute of Technology in my endeavors to secure a culture of this organism.

My attention has been called to the fact, that Dr. Davis has recently studied some cultures of *B. Influenzae* in your laboratory and as I do not know him personally, I take the liberty to write and ask, if you will kindly request him to forward me two or three type cultures of *B.*

Influenzae in order, that I may have them tested with my serum for agglutination, and should the reaction be obtained, I fully intend to be vaccinated with the cultures.

Trusting you will not find it inconvenient to comply with this request, I am with sincere regards,

Very sincerely yours,  
(Signed) James Carroll.

P. S. Kindly ask Dr. Davis or whoever may send the cultures to forward them by Express collect to me at my house address 1433 Clifton Street, North west.

Letter of James Carroll,  
May 1907.

Dear Docotor Hemmeter:

Of course you will have deemed me ungrateful and inappreciative of the great honor to be conferred upon me by the old University my honored *Alma Mater*. But it is not so; I have been sick in bed since Feb. 17th, running a temperature every day except for tree days, when it was temporarily controlled by aspirine. As I write now my temperature is above 100 (2 P. M.) and rising and I am sitting up contrary to the advice of my physicians friends. Nevertheless I have felt all along, that I would send nothing but an autograph reply and this I have delayed day after day in the hope, that I would soon gain sufficient strength to write a long and satisfactory letter. The visit of my dear friend, Dr. I. S. Stone, enabled me to rest more comfortably afterward, because I felt, that he would explain the circumstances to you. I am sorry to say, that during the past four or five days my heart has needed a little coaxing for all attempts to sit up proved too much, though I felt very well while lying down. With this explanation I trust you will pardon my apparent rudenes in thus delaying my response to a communication that made me very happy indeed. I assure you most sincerely that, apart from the personal affliction, it gives me the deepest sorrow to feel, that I am forced to be absent from such a happy and inspiring reunion. As it is, I feel, that if I am up about with a serviceable though damaged heart, within 30 days, that I shall have cause for further congratulation.

Permit me to express to you, as best I may, my humble appreciation of the high honor to be bestowed upon me, and the hope, that at some future date, I may be able to express my gratitude in person.

I one of your letters you ask for a list of publications, which I inclose: it will give me great pleasure to send you a set of such of the reprints as I have.

You ask whether I was infected as the result of our work. Certainly I was; I was the first to propose, that we submit and the first to be infected though not the first to be bitten.

I am sending by this mail a paper by my friend Dr. H. H. Donnelly and this may be relied upon as accurate in every particular.

There is no foundation in the report, that Dr. Reed aided me very materially in securing my medical education. As a matter of fact he had nothing whatever to do with it, and I was never associated with Dr. Reed in anyway, until I met him at the Army Medical School in Washington late in September 1893. The order for me to proceed there was issued upon the recommendation of Surgeon General Sternberg. At this time I had obtained my medical degree, had Hopkins (see Register 1891—1892 and 1892—1893) and had put in one summer working independently in the Army laboratory at the World's Fair in 1893, for which I hold a certificate.

Great is the Truth and it will prevail.

Believe me most gratefully,

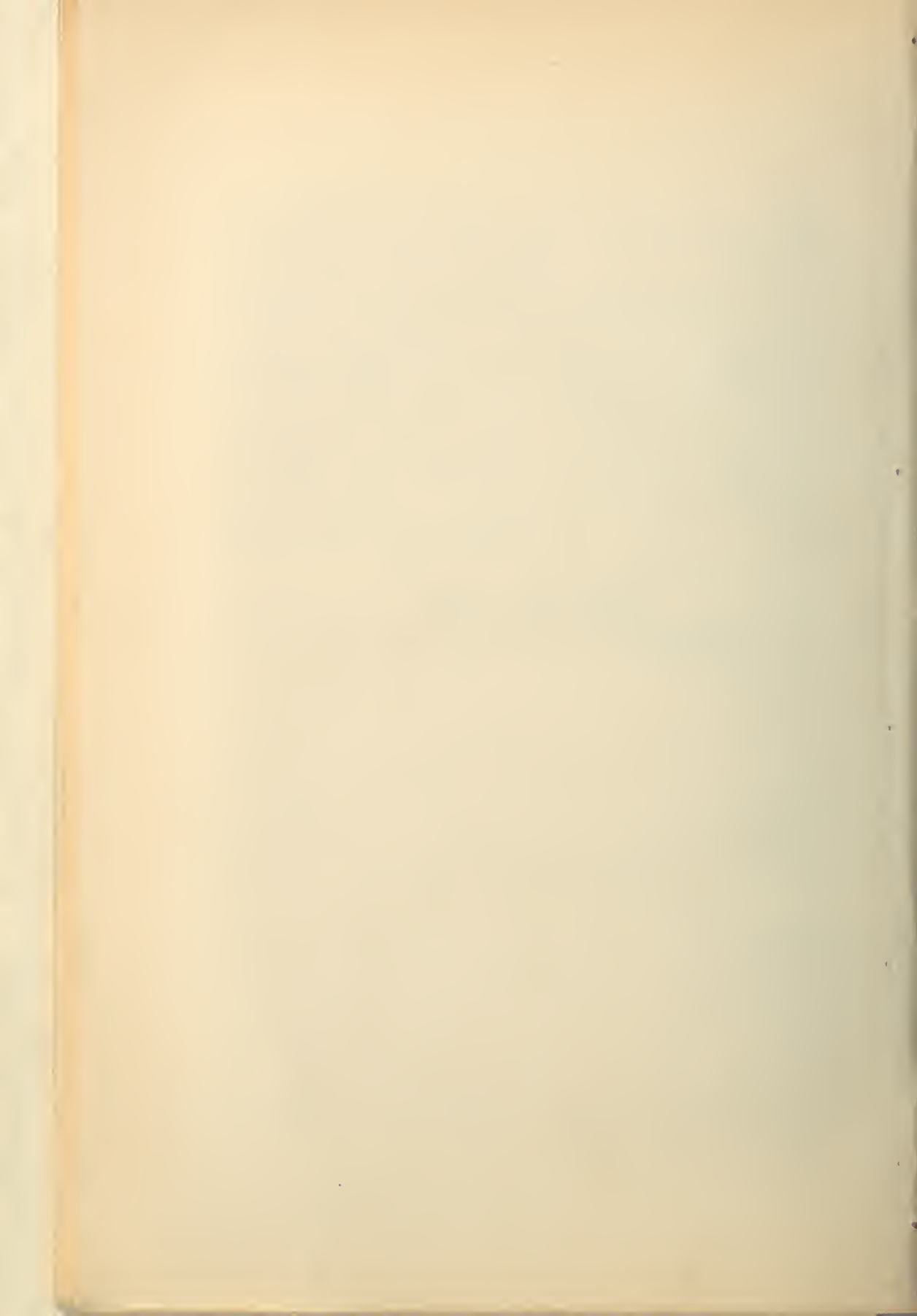
Fraternally and Sincerely yours,

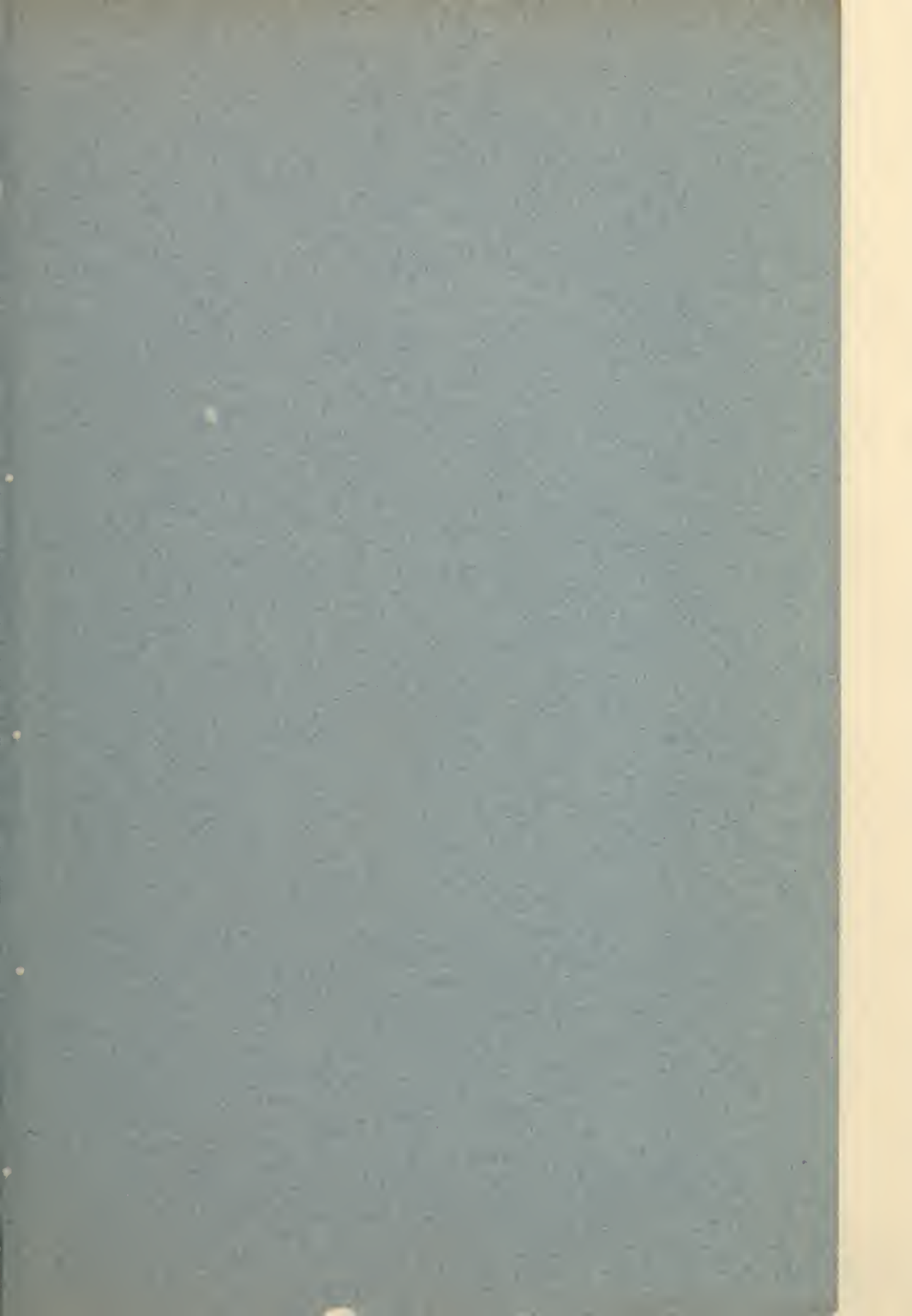
James Carroll.

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30

## INTESTINAL TUBERCULOSIS: TUBERCULOUS INTESTINAL NEOPLASMS AND TUBER- CULOUS ILEOCECAL TUMOR.

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JOHN C. HEMMETER, M.D., PHIL.D., LL.D.

Professor of Physiology and Clinical Medicine, University of  
Maryland.  
BALTIMORE.

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Nowadays, as much as in the time of Socrates, a great many of the difficulties in our advancement toward truth are due to errors of conception. By the teachings of this man a school of philosophers arose—the dialecticians, who spent their lives in discussions and considerations, aiming at the most exact definitions of words and the limitations of concepts.

Neglect of exactness in defining just what is meant by certain terms in pathology renders infirm many of the statistics quoted in the literature of tubereulosis.

Human tuberculosis may assume so many different forms, its progress and terminations are so heterogeneous, that great difficulties may occasionally arise, when it becomes necessary to decide whether a given pathologic process belongs to tubereulosis or some other affection. For instance there was a temptation to class a peptic ulcer of the stomach which was found in a case of pulmonary tuberculosis at postmortem examination as a tubercular ulcer, but as it had the typical structure of a peptic ulcer it was recorded as such. If macroscopic examination showed no enteritis, ulcers, enlarged glands, no cicatrices, caseation, calcification or adhesions, all suspicious pieces of mucosa were hardened in Zenker's fluid, and after paraffin embedding, serial sections were made.

In Naegeli's 63 lethal cases of adults, the intestine was tuberculous 28 times secondarily; the mesenteric glands were affected in only 5 cases.<sup>1</sup> It is difficult and almost impossible to determine the portal of entry of the tubercle bacillus from the observations gained at autopsy, or even on microscopic examination.

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1. Virch. Arch., 60, p. 465.



The rare congenital cases of tuberculosis are lethal in early childhood. The demonstration of tubercle bacilli was only attempted in one-half of my cases; if the macroscopic and microscopic picture is typical of tuberculosis, the demonstration of the bacilli is unnecessary, and the eventual failure to find them would not invalidate the diagnosis, provided the histologic architecture typical of tuberculosis were found. To the experienced, the difficulty in finding tubercle bacilli in old cases of tuberculosis is well known. If the diagnosis depended solely on the demonstration of tubercle bacilli, the old and healed cases would be lost for the statistics.

Caseation in mesenteric and intestinal lymph glands can safely be classed as due to tuberculosis. Gummata and lymphosarcoma, and actinomycosis may produce a form of necrosis difficult to distinguish from tuberculous caseation macroscopically, but not difficult to distinguish microscopically. Calcification of mesenteric lymph glands has been attributed to typhoid fever by Schüppel; proof of this assertion is difficult to bring. The proof that calcification is the result of a preexisting tuberculous caseation is furnished by serial section studies of the apices of tuberculous lungs. In the lungs of tuberculous subjects dying at ages from 18 to 35, caseation predominates (bronchial glands); but in tuberculous subjects dying in the years from forty to forty-five or later, one finds, as a rule, calcification in the same regions. This indicates that calcification is a later development from preceding caseation.

In fifty-six personal studies of the intestines of persons dead from pulmonary tuberculosis, the intestines were found diseased in all. I followed very closely Naegeli's method.<sup>2</sup>

The following is a synopsis of the results of detailed examination of the alimentary canal, mesentery and omentum in these 56 cases. Sections were made also through lymph glands in the mesentery and retroperitoneal glands:

**Tuberculous Enteritis:** In 30 cases there was diffuse tuberculous enteritis or catarrh, showing unmistakable tubercle with giant cells. Among these were 4 cases that had tuberculous mesenteric glands, 4 with tuberculous retroperitoneal glands; and in 6 cases simple enteritis, jejunitis, ileitis or colitis, not showing tuberculous architecture, were found.

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2. Virch. Archiv., vol. clx, p. 426.

**Tuberculous Ulcers:** In 14 cases there were tuberculous ulcers of the ileum and colon; two of these 14 had cicatrices in the lower third of the ileum about 10 inches from the ileocecal valve. In these 14 cases of tuberculous ulcers there was simultaneously more or less intestinal catarrh, but not diffuse, more localized in the lower ileum. One of the patients had been operated on for fistula in ano.

**Tuberculous Glands:** In 10 cases there was tuberculosis either of the mesenteric, omental or retroperitoneal glands. In 6 of these, the entire intestinal mucosa was intact; in the remaining 4 of these 10 cases there was slight circumscribed catarrh, enteritis or colitis, but the histologic examination did not reveal the characteristic structure of tubercle, in pieces excised from the catarrhal area. The peritoneum was found to present minute tuberculous nodules in but two cases of the entire fifty-six.

**Chronic Hyperplastic Tuberculosis of the Intestine** (*Tuberculose intestinale à forme hypertrophique* of French authors): The condition of chronic hyperplastic tuberculosis was found but once by myself, during an autopsy at Bay View Asylum, Baltimore. In macroscopic and microscopic appearance this tumor corresponded very closely to that described by Lartigau.<sup>3</sup> Lartigau's article contains the most important references concerning this subject (79 in all), which were obtainable at the date of that publication. It is highly probable that cases of cancer of the cecum that have been reported as cured after resection were instances of hyperplastic tuberculosis. The histologic detail and etiology are fully given in the article by Lartigau, but as the diagnosis is of importance, it will be considered in some detail in the following, which concerns more specifically the tuberculous cecal tumor, but applies also to the very closely allied condition of hyperplastic tuberculosis, for clinically and histologically they are generally inseparable.

#### TUBERCULOUS INTESTINAL TUMORS.

**Tuberculous Cecal Tumor:** It has already been stated that enlarged retroperitoneal and mesenteric tuberculous glands may simulate intestinal tumors. I wish to refer, especially, however, to the tuberculous tumor of

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3. Jour. Exper. Med., vol. vi, p. 23.

the cecum and appendix. The cecum, on account of its position, is the most favorable location for the arrest and deposit of tuberculous products which travel down the intestinal canal. The pulmonary tuberculosis which is observed, together with this intestinal complication, is frequently insignificant. Tuberculosis of the cecum, with advanced pulmonary phthisis, is a very rare occurrence. The recognition of tuberculous neoplasms in this region is a modern diagnostic advance, and must largely be credited to abdominal surgeons. Attention was first called to it as a disease to be differentiated from carcinoma of the cecum.

Among the first to differentiate these two conditions was Durant, cited according to Conrath.<sup>4</sup> The fact that Durant's article was published as late as 1890 is sufficient evidence that the recognition of this condition is a very recent one. In 1891 Billroth<sup>5</sup> called attention to the tuberculous character of certain ileocecal tumors. Czerny,<sup>6</sup> König,<sup>7</sup> Conrath,<sup>4</sup> Hofmeister,<sup>8</sup> Hartmann and Pilliet<sup>9</sup> and Salzer,<sup>10</sup> have contributed to our knowledge of tuberculous ileocecal tumors.

Tuberculous cecal tumor may originate in two ways: (a) From the mucosa, by extensions from tubercular ulcers on the inner side of the intestinal canal, and (b) from the serosa by the extension of tubercular lymph glands. The form that originates from the mucosa represents, no doubt, an autoinfection by means of tuberculous sputa. Whether or not the tumor may arise as a primary tuberculous process from ingested tuberculous food cannot definitely be stated, and Koch's recent utterances<sup>11</sup> cast a doubt on this question. In most cases, the tumor results from three forms of changes incident to the tuberculous infection: (1) The inflammatory infiltration as a consequence of multiple tuberculous ulcers which (2) may lead, partly, to extensive scar formation, and, by cicatricial contraction, cause stenosis of the lumen and (3) hypertrophy of the intestinal walls as a result of the stenosis.

As to the relation of this condition to appendicitis

4. Brun's Beitr. z. Chir., vol. xxi, No. 1, 1898.

5. Wien. med. Presse, 1891, p. 193.

6. Brun's Beitr. z. Chir., vols. vi and ix.

7. Deutsche Zeitschr. f. Chir. vol. xxxiv. 1892, p. 65.

8. Brun's Beitr. z. Chir., vol. xvii, 1896, p. 577.

9. Bull. de la Soc., anat. de Paris. 1891. p. 471.

10. v. Langenbeck's Arch., vol. xliii.

11. Congress on Tuberculosis, London, 1901.

and perityphlitis of tuberculous origin, it may be stated, briefly, that among 120 cases of perityphlitis Langfeldt found that 20 were due to tuberculous processes. The chief stenosis occurs at the ileocecal valve, the folds of the valve being involved in the process. Professor W. P. Obrastzow, of Kiew,<sup>12</sup> calls attention to the fact that stenosis of the ileocecal valve does not always bring about a collapsed and contracted condition of the ascending colon. Theoretically, one would expect to meet with this result, and one ought to find that the ascending colon would be palpable, if at all, as a thin band or cord. In some cases, this is really the condition found on palpation, but the colon in other cases is found as a distended cylinder about five centimeters in diameter. Obrastzow attributes this distension to the production of gases from stagnating intestinal contents.

#### THE DIAGNOSIS OF TUBERCULOUS CECAL TUMOR.

Conrath<sup>13</sup> collected 85 cases, of which 65 per cent. were between the ages of twenty and forty years. In its incipency the disease is latent; there may be constipation or constipation alternating with diarrhea. The disease is, as a rule, not recognized as serious until the symptoms of stenosis are apparent. Then follow either localized or diffused pains of an acute, colicky character. Above all, persistent constipation, nausea, vomiting and frequently visible intestinal peristalsis occur. Hemorrhage from the intestine, in the form of hemorrhagic admixtures in the stool, are rather frequent. As the disease is a complication of pulmonary tuberculosis, elevation of temperature is met with frequently.

Obrastzow, in a more recent and very scholarly contribution to the subject<sup>14</sup> looks upon an early and rapid development of the stenosis in the cecum as carcinomatous, and a late and slow development is considered by him as characteristic of tuberculosis. In three operated cases of carcinoma of the cecum, the stenosis developed in the course of from three to nine months from the beginning of the disease. In ten cases of tuberculosis of the cecum, the stenosis developed in the course of from three to nine months from the beginning of the disease. In ten cases of tuberculosis of the cecum, the

12. Arch. f. Verdauungsk., vol. iv. p. 440, Zur Diagnose des Blinddarmcarcinoms, der Blinddarmtuberkulose., u. s. w.

13. Quoted from Hemmeter's Dis. of Intestines, vol. ii.

14. Arch. f. Verdauungsk., vol. vi, p. 23.



phenomena of stenosis were at no time very pronounced.

In the differential diagnosis we must consider the possibility of : (1) Cecal carcinoma; (2) dislocated kidney; (3) fibrous appendicitis; (4) accumulated scybala in the cecum.

The differential diagnosis from cecal carcinoma is more precisely stated in the subjoined table.

From dislocated kidney, cecal tuberculosis is distinguished by the following signs: The dislocated kidney is more moveable; it gives a dull sound on percussion, and is very rarely accompanied by signs of intestinal stenosis; a diseased kidney, when affected with carcinoma, tuberculosis, gonorrhoeal infection or calculi, gives rise to nephralgia, pyuria, hematuria, etc. A dislocated kidney can usually be replaced into normal position.

The main supports of the diagnosis of tubercular cecal tumor are: (1) Infiltration of the walls of the cecum, which assumes the character of a tumor; (2) the presence of tubercle bacilli in the stools. In the beginning, the tumor is more or less movable, but later on it may become fixed by adhesions or contracting bands in the mesentery. The lower edge of the cecum is located one centimeter above the interspinal line in man, but when it becomes diseased by tuberculosis or carcinoma, the lower border of the cecum rises four centimeters above the border of the linea interspinalis. In these cases, therefore, the cecum is found in the upper part of the iliac fossa, or even above the crest of the ileum. Obrastzow explains this high position of the cecum under such conditions by a shortening of the intestinal tube caused by a sclerotic process of a tuberculous nature. As a consequence of this high position of the cecum, the ileum is palpable for a considerably longer distance than it would be under ordinary conditions. Purulent disintegration of the tumor may lead to the establishing of abscesses communicating with the peritoneal cavity or adjacent organs, or it may cause a break externally causing a preternatural anus. The course is protracted, particularly as the disease is generally not recognized in its incipency; cases have been observed that lasted three years.

Krokiewicz<sup>15</sup> has made extensive investigations concerning the value of the Ehrlich diazo reaction in the differential diagnosis between carcinomata and tuber-

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15. Wien. klin. Wochschr., 1898, No. 29.

culosis of the intestinal tract. According to his results, the diazo reaction is generally present with intestinal tuberculosis, but is absent in carcinoma. The diagnosis of cecal tuberculosis thus rests partially on the presence of the Ehrlich diazo reaction, together with other signs and symptoms already referred to.

The other rare conditions with which this disease might be confounded are actinomycosis, sarcoma, fibroma; foreign bodies, fecal concretions and intussusception. Scybala, or fecal concretions, are rarely found limited to the cecum. If they are present there they can be palpated throughout the colon. The only fecal concretion that could confuse the diagnosis would be one that is limited to the cecum. If necessary, the colon could be washed out by a high irrigation, which, after several repetitions, would eliminate the possibility of scybala.

The distinction from fibrinous appendicitis can frequently not be made, except by observation of the course of the disease. Improvement will follow in appendicitis of this chronic type, with a palpable induration in the right iliac fossa, on proper treatment in bed, external application of heat, counter-irritation and careful diet; but the tubercular cecal tumor will not improve under such treatment. Fibrinous appendicitis is not a concomitant of pulmonary tuberculosis, whereas the tubercular cecal tumor is always secondary to pulmonary tuberculosis.

The following schema, which is adopted from Boas' *Verdaunungs-Krankheiten*, page 291, may serve to distinguish between carcinoma and tuberculosis of the cecum:

Cecum Tuberculosis.	Cecum Carcinoma.
<i>Age</i> : Between 20 and 40 years.	<i>Age</i> : Rare before fortieth year.
<i>Duration</i> : From 2 to 3 years.	<i>Duration</i> : Eight to nine months.
<i>Lungs</i> : Pulmonary tuberculosis evident more or less.	<i>Lungs</i> : Negative.
<i>Tumor</i> : Elongated; the intestine is palpable as an infiltrated thickened cylinder.	<i>Tumor</i> : Sharply circumscribed, intestines not palpable.
<i>Stenosis</i> : Always present, develops slowly, accompanied by striking, splashing and musical sounds.	<i>Stenosis</i> : Develops rapidly, acoustical signs not so pronounced.
<i>Stool</i> : Blood and pus rare, tubercle bacilli frequently present.	<i>Stool</i> : Blood and pus frequently observed; tubercle bacilli absent.
<i>Fever</i> : Generally present.	<i>Fever</i> : Exceptional.
<i>Urine</i> : Ehrlich's diazo-reaction positive.	<i>Urine</i> : Diazo-reaction negative.

**Prognosis:** This is grave under all conditions, and

conditioned by the consequences of the diseases that have been described above, the principal one being stenosis, disseminated intestinal or peritoneal tuberculosis, multiple abscess formation, and amyloid degeneration of the kidneys and intestines. The pulmonary tuberculosis in itself is one which makes the outlook hopeless.

**Prophylaxis:** The prevention of primary local infection calls for sterilization of all food, particularly of unboiled milk, avoidance of association with tuberculous patients, particularly of tuberculous nurses in the case of children, and the avoidance of autoinfection by the swallowing of sputa. Enteritis in tuberculous individuals should be treated with great care, as the mucosa which has become diseased is more liable to tubercular infection than a healthy one.

**Treatment:** The treatment of tuberculous enteritis or of enteritis and colitis in tuberculous patients, even where it can not be proved to be a tuberculous infection localized in the intestine, demands a diet similar to that described in my work on "Diseases of the Intestines" for enteritis, colitis and dysentery. Strained soups, made of oatmeal, bouillon and egg, with salt, together with acorn cocoa and a little claret, should constitute the sole articles of diet for about twenty-four hours. The patient should be confined to bed. If an error of diet can be distinctly made out, a small dose of calomel, one-half of a grain, repeated every three hours, and combined with one-sixth of a grain of denarcotized extract of opium, will hasten the evacuation of the offending food.

Concerning the specific treatment of intestinal tuberculosis by tuberculin, I may say that there is no doubt that a number of patients have been cured by a cautious administration of this substance. I have personally studied the healing of a tuberculous rectal ulcer under the influence of tuberculin; nevertheless, I do not recommend the systemic employment of tuberculin in the treatment of tuberculous intestinal ulcers, enteritis, or cecal tumor, because this form of treatment has not yet been satisfactorily tested for intestinal diseases, and also because of the undesirable effects tuberculin occasionally exerts on other organs, which also demand consideration. For the diarrhea, tannigen, tannalbin, bismuth subgallate and bismuth salicylate, as well as naphthalin, have proved useful in my experience, but I must emphasize that nothing beyond a temporary relief must

be expected of these remedies. The creosote preparations have, in my experience, not proved useful. The frequent eructations which creosote causes, when given in the doses recommended for these patients, reduce, rather than increase, the appetite. The only partial success in the way of treatment of tuberculous ileocecal tumor is to be expected from operation, wherever this is possible.\*

PERIBRONCHIAL GLAND TUBERCULOSIS TRACEABLE TO A PRECEDING INTESTINAL INFECTION.

One of the earliest experiments showing that general infection of tuberculosis could occur by the way of the intestines as the portal of entry, and yet leave no evidence of tuberculosis in the intestines was made by Orth in 1886<sup>16</sup>. The literature of this subject is given by Mazyck P. Ravenel.<sup>17</sup> In the light of the experiments of Ravenel, we are warranted in concluding that under certain conditions tubercle bacilli pass through the normal intestinal wall with great facility and rapidity. The most favorable condition for this to take place appears to be during the digestion of food made up largely of fat. When we remember that the chyle is carried directly into the blood stream through the thoracic duct, it is easy to understand how it is that infection through food may show itself first in the lungs, or at any rate, that the lesion in the lung may be as old as the intestinal lesion.

The claim that alimentary tuberculosis should show itself in a primary intestinal lesion is fallacious and misleading. Cats which are fed with virulent tubercle through a catheter, will in from six to ten days after-

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\* General tuberculous peritonitis that arises from or is consequent to tuberculosis of the cecum or appendix can not be successfully treated except by operation. In my article on "Diseases of the Gastrointestinal Tract on the Borderland Between Surgery and Internal Medicine," *Med. Record*, New York, Nov. 16, 1907, I present clinical records of cases of tuberculosis of the peritoneum treated by operation and others treated by conservative or expectant methods. My conclusions were that as many cases recover without operation and remain cured, as with operation. This statement can only be understood, however, when studied in connection with other facts given in this paper. The curability of tuberculosis of the peritoneum without operation does not refer to that form that arises from tuberculosis of the cecum, appendix, genitourinary organs, and direct extensions of the tuberculous process through the walls of the digestive canal. These cases require experienced diagnostic analysis and as far as can be foretold at present will continue to be the proper cases for operation.

16. *Specielle pathologische Anatomie*, vol. i, p. 839.

17. *Jour. of Med. Research*, vol. x, 1903, p. 460.



ward give evidence of a tuberculous peribronchitis, in about 75 per cent of the animals infected, so that I have come to regard a peribronchial tuberculosis, without any severe lesion in the parenchyma, as an infection that has taken effect through the intestinal walls. The so-called tuberculosis pulmonum peribronchialis,<sup>16</sup> is due to an original infection through the alimentary canal.

Mazyck P. Ravenel<sup>17</sup> has demonstrated that the tubercle bacillus will pass through the stomach unscathed if it is taken into the digestive tract, mixed with food rich in fats; thus it will be able to cause intestinal infection if it is taken in a certain amount of oil.

This leads us to consider an interesting bit of pathologic physiology.

It is well known from the researches of Pawlow, that fats and oils arrest the secretion of gastric juice,<sup>18</sup> especially of hydrochloric acid, which is the normal disinfectant of the gastric contents; milk is chiefly an emulsion of fats, and from the studies of Pawlow we know that milk causes a less secretion of hydrochloric acid than any other food. It is, therefore, most likely to prevent the secretion of the very substance which could destroy the tubercle bacilli contained in it. For this purpose, it is advisable to recommend the use of dilute hydrochloric acid to tuberculous patients, or even to those who are not yet tuberculous when gastric secretion is impaired, in order to prevent the infection of the intestines.

The passage of tubercle bacilli through the uninjured intestinal mucosa was first demonstrated by Dobroklonski,<sup>19</sup> in experimental infections of rabbits. Lartigau<sup>3</sup> has also confirmed this statement.<sup>20</sup>

18. Arbeit der Verdauungsdrüsen, p. 135.

19. Arch. d. med. exper. et d'anat. path., 1890, ii, p. 253.

20. In addition to the authorities cited, the following references may be consulted:

Körte: Deutsche Zeitschr. f. Chir., vol. xl, 1895, p. 523.

Eisenhart: "Ueber Häufigkeit und Vorkommen der Darmtuberculose," Diss. inaug., München, 1891.

Wittstock: "Zur Klinik des Ileus durch Darmtuberculose," Diss. inaug., Berlin, 1893.

Buttersack: "Zeitschr. f. Tuberculose u. Heilstätten Wesen," November, 1900.

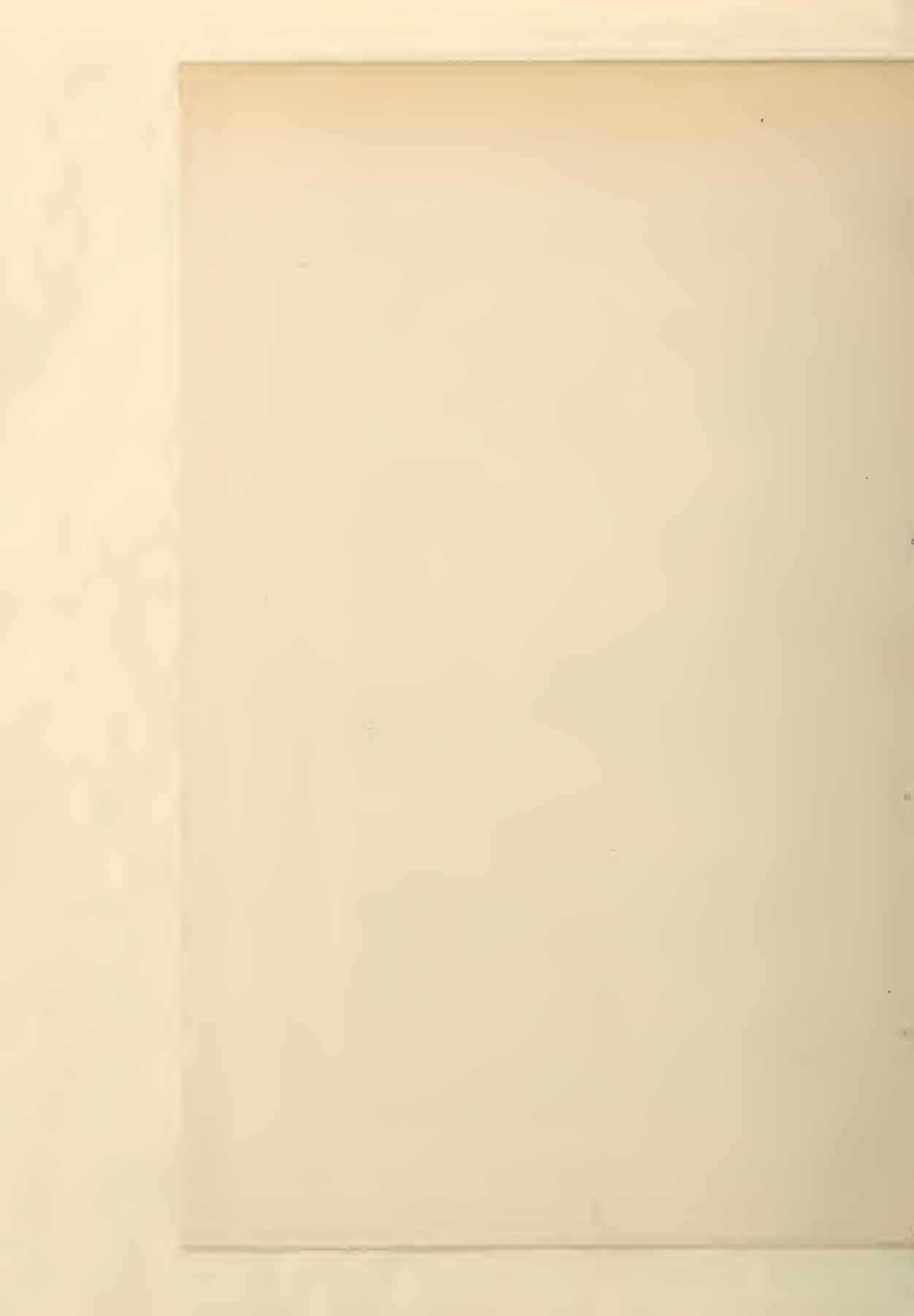
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Reprinted from the Journal of the American Medical Association, February 29, 1908, Vol. I, p. 655-658.

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SCIENTIFIC, LITERARY, AND POETICAL  
ACTIVITY.

By JOHN C. HEMMETER, M. D., PH. D.





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Albrecht von Haller was born October 18, 1708, at Bern, [65] Switzerland. He was the fourth and youngest son of the attorney-at-law, Nicholas Emanuel von Haller. According to his own biography and the statements of his most reliable biographers, Ludwig Hirtzel and Jacob Baechtold,<sup>1</sup> he was possessed of extraordinary and precocious powers of observation, versatility in language, poetic talent, and unusual industry in collecting facts and objects. He is said to have been a very weakly, timid, and always serious child, and was taught by an old pedantic theologian, whose curious character aroused the satiric, poetic power of his tantalized pupil.

Haller himself narrates to his oldest biographer that at the age of nine years, he had produced an extensive lexicon of all the Hebrew and Greek words of the Old and New Testament, a Chaldaic grammar, and between one and two thousand biographies of distinguished personages.

However incredible these statements may appear, Ludwig Hirtzel, who, according to my friend, Professor Henry Wood of the Germanic Department of the Johns Hopkins University, is an absolutely reliable biographer, gives an authentic poem of Haller's of the year 1721, which is an elegy on the death of Frisching. The poem was written then when Haller was 13 years old, and in its title the poet calls himself a "poet who is a lover of virtue and disciple of wisdom."

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<sup>1</sup> Geschichte d. Deutschen Literatur in d. Schweiz, p. 489.

[65] Whilst this poem does not show the perfect rhythm and majestic sentiment of the poems of his later years, it is nevertheless an effort that must be considered genuinely poetic.

In 1722 he left his native city and became a student under the physician John Neuhaus in Biel, who was a worshipper of the doctrines of Cartesius (Descartes), which, however, repelled his brilliant pupil.

At that time Haller was 14 years old, and now we are told of his first morbid inclination. He was continuously sick, avoided playmates, locked himself up for months and consoled himself with poetry in various languages. He wrote a long epic poem on the Origin of the Swiss Union of States, several tragedies, and translated Ovid, Horace, and Virgil. As another evidence of a morbid inclination, the facts may be cited that he once saved this mass of verse and literary compilation from a burning house at great risk, but later on he burnt them up, part and parcel.

In 1723 he went to the University of Tübingen, but was not well impressed with the rushing student life there, nor made much progress in his special studies, and in April, 1725, he [66] went to Holland to study under the renowned Boerhaave at the University of Leyden. A month before his departure, as Haller himself writes, he composed the beautiful hymn "Morning Thoughts." This is an apotheosis on the Omnipotence of the Creator and is undoubtedly one of the most impressive poems in the German language. A few lines to illustrate this poem may be pardoned:

Der Mond verbirget sich, der Nebel grauer Schleier  
Deckt Luft und Erde nicht mehr zu;  
Der Sterne Glanz erblaszt, der Sonne reges Feuer  
Stört alle Wesen aus der Ruh—  
Durchs rote Morgentor der heitern Sternenbühne  
Naht das verklärte Licht der Welt;  
Die falben Wolken glühn von blitzendem Rubine  
Und brennend Gold bedeckt das Feld.

And then our poet, addressing the Creator of Nature, continues:

Du hast der Berge Stoff aus Thon und Staub gedrehet  
Der Schachten Erz aus Sand geschmelzt;  
Du hast das Firmament an seinen Ort erhöht,  
Der Wolken Kleid darum gewälzt.

At that time Boerhaave was in the fullness of his power. [66] The maturity of his broad experience undoubtedly laid the foundation of all the future works of Haller, but here Haller met two other men of scientific greatness; the younger Albinus, Frederick Bernard Albinus, a skillful and sagacious anatomist, who in 1745 became Professor of Anatomy; and also Ruysch, who was his teacher at 90 years of age. He took his degree of Doctor of Medicine in 1727 at Leyden on the basis of a thesis in which he exposed the error of Professor Coschwitz of Halle, who had maintained that he had discovered a new salivary duct of the submaxillary and sublingual glands, which Haller proved to be a vein. Thereafter he traveled extensively in England, visited Belgium and Paris in 1728, and studied mathematics in Basel with Bernouilli. In 1730 he returned to Bern and there practiced medicine and continued his researches in anatomy and physiology, spending his leisure hours in noting down poetic inspirations and making botanical explorations. In 1736 his fame had spread to such an extent that George II of England, who was also Elector of Hanover and Braunschweig, offered him a chair of anatomy, botany, and medicine at the newly-founded University of Göttingen. Haller accepted, and labored in Göttingen for 17 years, carrying out his most important inquiries and compiling most of his literary work. He founded the anatomical museum and laboratory, the botanical school and garden, and the obstetrical department at Göttingen. He was one of the founders of the scientific association and editor of its commentaries. Later on, he refused several calls to other universities, noteworthy among which was one by Frederick the Great, to a chair at the University of Berlin.

He returned to Bern in 1753, prompted partly by illness and partly by ambition for official station in his Fatherland. In Switzerland he passed the last 24 years of his life, taking his share of municipal and state duties. He eventually was elected a member of the great National Council of Switzerland.

Towards the last years of his life, persistent severe pain led him to the continuous use of opium. He passed quietly away on December 12, 1777. In the last moments of his life he



[66] had his fingers on his own pulse and said to his friend, who was standing at his bedside, "The artery no longer beats."

Haller was married three times. His most extraordinary versatility as a poet, litterateur, political economist, botanist, physiologist, physician and surgeon, has been the wonder of his many biographers.

He applied his tremendous intellect to the solution of many questions throughout physiology, and in the preface of the sixth volume of his *Elementa*, he gives a list of what he claims as some of his own discoveries. There is no doubt whatever that he correctly recognized the mechanism of respiration, and his researches on the "formation of bone" and the "development of the embryo" are of the highest importance.

#### HIS LITERARY AND POETICAL ACTIVITY.

In the year 1728, Haller, in company with a friend, traveled through his native country, which up to that time had been to him an unknown territory. The real object of this trip was not so much to observe the works of man as to get into communion with Mother Nature. In accordance with this plan he made a collection of rare specimens of the Swiss flora, and in fact everything, whether of high or low degree, became the object of his undivided admiration. Never did the uplifting thought leave him that God indeed had made everything beautiful, and devoted to some purpose in nature's economy. The glacier and the gentian, the tumbling brook and the dew drop, one and all, united our enthusiastic teleologist to God's service in His boundless temple of Nature.

The impressions made upon him were put into poetic form in the following year in a poem entitled "Die Alpen" (The Alps). Haller compared with biting sarcasm the low morality of his native town, Bern, with that of the old Swiss type, and thus emphasized his sympathy with Muralt's staid reformatory tendencies, revealed in the latter's "Letters about Englishmen, Frenchmen, and about my Journeys." He advises sufferers from the low morality of large cities not to seek recovery by going to Paris, but by travel to Switzerland where liberty and sincere morality prevail. Haller, the sentimental

precursor of Rousseau, calls the people of Switzerland happy [66] because of their ignorance about those evils which are the usual concomitants of growing cities. In his poem, in which he gives evidence of all that manly strength of which he is capable, and in which moreover he displays intense longing for pastoral quietude, he described the inhabitants of the Alps, not as peaceful Arcadian shepherds of the well-known stage type but as children of Nature, honest, unsophisticated people of the good old time. He praises their high ideals of matrimony, their harmless, good-natured festivities, their brawn, their various occupations as called for by the changing seasons, and brings all these things to the notice of the dwellers in cities. He pictures to us a beautiful landscape, surrounded by the Alps, which serve as a natural defence against the evil influence of the outer world. Winter ap- [67] proaches and you enter the hut high up in the mountains. Three generations gather around the fire-place—a young poet of nature sings his simple melodies, three older members follow him in turn, one speaking of the wonders of nature, and the others relating stories of heroism in the battles for independence, and praises:

Tell who removed with intrepid courage the yoke which is still borne by half of Europe.

Thus from the Swiss mountains resounds first the battle cry "In tyrannos," which Schiller, Haller's successor in many respects, so frequently used, Goethe having previously made use of a democratic motto from Haller for his "Goetz von Berlichingen." Liberty and decent moderation are the unflinching precepts in a poem which forms the sentimental and purposeful supplement to his "Vitiating Morals," and the satire "The Man after the World." The young citizen of Bern thus described his countrymen:

No, surely 'twas not so before France got to know us,  
Unknown to us were then the very names of crime;  
Harmful extravagance our poverty withheld.  
Sin in its wake was foiled by gentle singleness.  
We had one fatherland, one God, and one free heart;  
But now, alas — we fall!  
The courage of our citizens which sanctified a state

[67] The marrow of our fatherland grows old and dies away,  
And once again in history the world will surely read:  
How states must go to ruin when moral law they will not heed.

Later on he renounced his praise of these Alpine children of nature, for it subsequently became evident that the youthful traveler had transported himself in his poetic fervor to a beautifully conceived past, or to a place that existed merely in his fancy when he said that the shepherds prefer the sparkling water from the mountain spring to the golden wine, or the son of nature despises the gold sand in his rivers: "The shepherd sees this treasure, he merely looks at it and lets it float away." This sentimental bias and pessimistic view of civilized life was supplemented, however, by a very practical common sense view of nature on the one hand, and on the other by an exuberant optimism of a religious character. Haller believed, like Leibnitz and Pope, "Everything which exists is good and for the benefit of humanity." Thus the Alps furnish us in their vegetation with medicinal herbs, the mountains with crystals and curative springs, and the icy glaciers even are there for a purpose, in that they irrigate the surrounding country. In brief, the Creator has done everything for the best of humanity. But such doctrine made it incumbent upon him as a faithful follower of Leibnitz to work out a so-called theodicy, an explanation of God's indulgence in permitting the existence of evil at all. He good naturedly pacifies us with the assurance that God's divine kindness will work out everything for the best, whereby humanity, "the pitiable, intermediate type between angel and beast," does not become the wiser.

During the first half of the eighteenth century one fanciful theodicy followed another. The fearful earthquake of Lisbon in 1755 gave the optimists a severe blow. Voltaire, Haller's opponent, in a poem devoted to this awful catastrophe, referred to the latter as a terrible argument against the above-stated doctrine. Voltaire himself, had deduced the existence of God from the established order of creation, without resorting to such ridiculously trivial teleology as to praise the creator of the cork-tree as the furnisher of the highly useful stopper. His often quoted saying, "If there were no God he

would have to be invented, but all creation proclaims his (67) existence," should be treated with as much consideration as Haller's maxim—"Enough! There is a God, for nature doth proclaim it." But now the best sections of a flourishing city go to ruin, and in the deliciously satirical tale, "Candide," this pious hallucination is mercilessly scourged. Haller, who took pleasure in displaying his antagonism to Voltaire, had by that time already given up his poetic activity. One small volume of poems represents about the extent of it. It is this feature, in conjunction with an unusual intensity of thought, which gave to his "Swiss Poems" an epoch-making value. By way of contrast to a whole cluster of poetasters of the "quantity not quality" variety, a serious philosophic poet had made his appearance. These made rhymes after rhymes in quick succession; but he, conscientious about the wording of his verses and the creation of new forms wherever he felt the need of such, was content to complete about ten verses an evening. The former showered fulsome, insipid eulogies on their friends and patrons, but he pointed out the line of demarcation which separated his Nuptial Song to a Swiss Cato<sup>2</sup> from the usual cheap congratulatory poems. On the one side chaff, on the other side grain, although of a small quantity; on the one side dazzling raiment, on the other a heavy suit of armor; there prodigality, here economy, almost penury; there superficial amusement, here high ideals pertaining to life and its problems.

Haller was the first to impart force and depth to German poetry, even if he did not assist in bringing about facility of expression. One should read his truly great fragment "About Eternity," in which he portrays a desolate landscape, crags, sinister trees, a bird that has lost its way, and an idly-flowing brook—a spot where the lonely pilgrim directs his attention to the contemplation of eternity and is overwhelmed by the thought of a beginning without an end. But

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<sup>2</sup> Note by J. C. H.—M. Porcius Cato, the elder, was noted as a rigid judge of morals, and this Swiss Cato must have been of the same character.



[67] how can he, who is subject to finite conditions, comprehend the infinite:

On awful numbers I place numbers,  
And millions of mountains I heap;  
I roll cycles upon cycles and worlds upon worlds;  
And when from this tremendous height  
With trembling fervor I again thee seek,  
O God! All might of numbers  
Increased a thousandfold  
Is not yet a part of Thee!

Kant cites these lines of "the most sublime German poet" in his essay on the "Infinite in Creation." To regard life from [68] a pleasant point of view, to sing the songs of youthful gaiety, was foreign to Haller's ponderous nature. Inclined to loneliness, reserved and sensitive, lacking resiliency to experiences of a disagreeable character he kept aloof as he himself stated from a real understanding of the joy of youth. Love was to him the most serious occupation to which he devoted himself. Although penurious in his lyric effusions relating to it, he however created in his "Doris" the ideal of womanhood; his deeply-conceived elegies on the occasion of the death of his first wife and also on that of his second were evidences of his intense feeling. With this tearful offering Haller bid the world of poetry farewell.

As a Göttingen professor, soon afterwards Albrecht von Haller became famous throughout Europe as the "Great Haller." The Academy of Berlin sought him, but the free-thinking tendencies of Frederick's court were distasteful to the pious Christian. Possessed of immense learning, he devoted himself with indefatigable industry to scientific study. Histories of botany, physiology, and anatomy must each give him his due share of honor. An examination of the mural decorations of the exterior of the University of Vienna reveals his name as combining in one person the rarest abilities of the investigator and experimenter in the domain of natural science with an almost unattainable knowledge of literature, and withal pervaded by an unusual sense of modesty. He was a veritable encyclopedia of information, "*πολυμαθής*," wrote for many years reviews on books relating to all departments of knowledge, at one time appeared in the rôle of a theologian,

at another as a politician, and in his last period became a [68] statesman and administrator of public affairs. He rehabilitated the poetic and scientific fame of Switzerland. The very fact that a scholar of his type should not disdain to write a volume of poems, exalted poetry and the poet in the estimation of the people.

#### CONTRIBUTIONS TO ANATOMY AND SURGERY.

Albrecht von Haller must be mentioned as one of the first to investigate the etiology of septicæmia. He made the experiment of injecting putrescent substances into the veins of living animals, establishing the fact that they were rapidly killed thereby.<sup>3</sup>

In another direction he stimulated pure surgical research—namely, in an investigation concerning the development of a collateral circulation after the ligation of larger vessels—the larger anastomoses had in fact been made out by Haller.<sup>4</sup> Concerning echinococcus of the liver, Haller held the view that it was an exuberant formation of follicles.<sup>5</sup>

The founder of the surgery of the diseased states of the biliary passages was J. L. Petit, who recommended puncture of the gall-bladder for advanced stagnation of bile, and the removal of gall-stones by incision; but to make both operations feasible, he postulated the necessity of adhesion of gall-bladder with the abdominal wall. The first to support the views of Petit were Haller and Morgagni.<sup>6</sup>

Haller described exactly the invagination of the colon into the rectum and gave its differential diagnosis from rectal prolapse.<sup>7</sup> In writing the history of hernia as a pathological entity, it should never be forgotten that Haller clearly described the peritoneal process extending into the scrotum as the persistence of a foetal physiological formation; opposing the view of Reneaulme, then prevalent (since 1721) that it

<sup>3</sup> Friedrich Helfreich. *Geschichte d. Chirurgie*. In Neuburger's and Pagel's *Handbuch d. Gesch. d. Med.*, iii, 20.

<sup>4</sup> Loc. cit., p. 86.

<sup>5</sup> Loc. cit., p. 219.

<sup>6</sup> Loc. cit., p. 222.

<sup>7</sup> Loc. cit., p. 239.

[68] was an abnormal place for peritoneum, for he and J. Hunter demonstrated the protrusion of the peritoneum that preceded the descent of the testicle, and argued that in congenital scrotal hernia the intestinal loops must of necessity follow the same channel. Haller correctly described a large hydro-nephrosis discovered by him at autopsy.<sup>8</sup>

His principal achievements in anatomy were: 1, a demonstration that the salivary duct discovered in 1724 by Cosch-witz, was a vein; 2, an investigation of the respiratory muscles and an exhaustive description of the diaphragm, with an interpretation of the intercostal muscles as elevators of the ribs; 3, a demonstration of the uterine musculature; 4, a demonstration of the *coni vasculosi*, *Vasculum aberrans Halleri*; 5, a correct description of the musculature of the heart and an accurate description of the pericardium and of the valves in the veins; 6, a description of a number of unknown or, at least imperfectly known arteries (*Tripus Halleri*, triple branching of the *cœliac* artery, description of the course of the musculophrenic and of the internal mammary artery, anastomoses of the internal mammary with the intercostal artery); 7, the higher location above the pubes of the bladder in children; 8, a description of the omentum; 9, a demonstration of the *Tela cellulosa* as a connective tissue substance.

His successors in Göttingen were Johann George Roederer, 1726 to 1763; Johann Gottfried Zinn, 1727 to 1759, and Heinrich August Wrisberg. Zinn and Wrisberg, two undoubtedly brilliant anatomists, were direct pupils of Haller. Zinn has become immortal through his classical description of the eye and its surrounding *Zonula* of Zinn (ligament of Zinn). This illustrious pupil of Haller became professor of medicine and director of the botanical gardens in Göttingen, 1753 to 1759.

The Swiss clinician, John George Zimmermann, was also a pupil of Haller. Both Zinn and Zimmermann assisted him in his investigations concerning the brain. Among the successors at Göttingen was Samuel Thomas Soemmering, 1755

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<sup>8</sup> Loc. cit., p. 276.

to 1830, whose comprehensive text-book is a monument in the [68] history of German anatomy. Soemmering was undoubtedly the most talented German anatomist at the beginning of the nineteenth century. Among the other intellectual descendants of Haller are Johann Friedrich Blumenbach, the founder of modern anthropology, and Johann Friedrich Meckel. Thus Haller's influence extended to the entire anatomical world of [69] his period.

Concerning the functions of the Eustachian tubes, however, he did not recognize the full truth, for he believed them to serve the conduction of sound and not as Schellhammer experimentally proved in 1716 for ventilation of the tympanum.

Exact medical historic research must credit Haller with a valuable discovery concerning the anatomy of the eye, for he was the first to describe the "lamina cribrosa" at the entrance of the optic nerve into the eye-ball (see Comment in Boerhaavii prælectis Götting. 1749), and he also, as well as Zinn, made clear the structure of the choroideal tract in the eye,<sup>9</sup> but he again failed to grasp the actual fact when he denied the existence of muscle fibers in the ciliary body and that they could influence the size of the pupil. But in this error he had investigators no less noted than Morgagni, Zinn, and Fontana as companions. Whilst he paved the way for a correct physiology of vision by his doctrine of the irritability of nerves, he seems to have failed in grasping what was known of refraction. As I understand Haller (*Elementa Physiologica*, Lib. XVI) he regarded light as a form of matter and ascribed to it a remarkable degree of substantiality.<sup>10</sup> Although he attributed refraction erroneously to contraction and dilatation of the pupil, his conception of the projection of the visible object on the retina was correct. It was a valuable service to the physiology of vision to emphasize the retina as the organ for light perception and not the choroid as Mariotte had argued previously.

Haller's analytical thinking and patient observation gave much new information in regard to neurological and mental

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<sup>9</sup> C. Horstmann. *Geschichte d. Augenheilkunde*, pp. 496 and 497.

<sup>10</sup> Vide supra, p. 499.



[69] diseases that eventually led to searching inquiries. In his *Elementa Physiologica*<sup>11</sup> he not only compiled that which was of interest up to that date, but added his own rich experiences and observations at autopsies. He emphasized that the brain was abnormal in all diseases of the mind and that the pathological alterations frequently extended to the cord and nerves, and he asserted that if nothing abnormal could be detected in these parts in rare cases, it should not be concluded that they were normal, but he preferred to think that the disease process was located in the "finest organizations" of these parts or that perhaps the examination had not been exact or careful.

The history of the development of gynecology would not be complete without including his anatomical, physiological, and pathological contributions, which are embodied in part of the 28th book of the *Elementa Physiologica*.<sup>12</sup>

#### CONTRIBUTION TO THE PHYSIOLOGY OF CIRCULATION AND RESPIRATION.

One of the most definite facts of this greatest of modern medical encyclopedists, and a fact upon which all later anatomists and physiologists agree, is that by his exhaustive work in anatomy and physiology references to literary sources earlier than his time have not only been greatly facilitated but in great part have been made superfluous; *i. e.*, one need as a rule only refer to his writings to learn the views of his predecessors on any important fact in these subjects.

In his preface to his *Elementa* he opposes the separation of anatomy and physiology—for him they were inseparable and yet he himself was the first to make physiology independent by his objective way of thinking and the significance he gave to experiments on the living animal. Sir Michael Foster correctly says:<sup>13</sup> "When we turn from any writers of physiology preceding his time and open the pages of Haller's '*Elementa*,' we feel that we have passed into modern times."

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<sup>11</sup> Lib. XVII, Sect. I, par. 17, Tom. V, Lausanne, 1763.

<sup>12</sup> Bernae, 1765; *Mulierbia*: Sectio II, *Uteri fabrica*.

<sup>13</sup> *Lectures on the History of Physiology*, p. 207.

Microscopic work with higher powers was quite unknown to [69] Haller, but all that could be observed by anatomical investigation simply,—even general histology,—whatever could be elicited by simple vivisection with the application of the means of stimulation known in those days—all that could be accomplished by these means are described in his *Elementa* in words that even to-day retain their full meaning; his facts are critically weighed and he cites the complete literature known to him.

The finer anatomical and physiological techniques of to-day were not dreamt of by him, and those processes of living matter that could only be studied by the methods and in the light of the chemistry and physics of those days were necessarily incorrectly or incompletely understood. In a study of the dynamics of the circulation whose foundation was laid by Harvey, Bellini, and Bovelli, or even earlier by Michael Scriverus, Mathæus Realdus, Columbus, and Cesalpinus,<sup>14</sup> the work and views of Haller are noteworthy. He was the contemporary of the versatile English divine Stephen Hales (1677 to 1761) a man whose mind was replete with original thought. His work on the physiology of plants and on hygiene is exceptionally meritorious, and in his work on "Hemostatics"<sup>15</sup> Hales describes his classical experiment of determining the hydrostatic pressure of the blood by tying a long straight glass tube into the artery of a horse. Singularly enough Haller, though familiar with this pioneer contribution, does not appear to estimate it sufficiently or correctly; in fact he does not cite Hales in his discussion of arterial pressure, although he makes use of his observations in his consideration of means "to determine the force of the ventricular systole," which perhaps was permissible in those days, for soon after more direct methods became available for this study.

Haller discusses exhaustively the determination of circulation time. He denies the so-called self-regulating mechanism of the heart, the coronary circulation, and even disproves

<sup>14</sup> Hemmeter. Johns Hopkins Hospital Bulletin, 1905, XVI, 165.

<sup>15</sup> Statical Essays, Vol. II, 1732.

[69] it. This controversy arose again in the nineteenth century between Hyrtl and Brücke.

[70] In his description of the changes of the form of the heart during contraction and the cardiac impulse, he lays more emphasis on the changes of form than did Harvey. He shows familiarity with the influence of gravity and of the respiratory aspiration of the thorax on the circulation in the veins.

One of his most brilliant experiments as well as arguments is the demonstration of the automatism of the heart. Anatomists, physiologists, naturalists, and medical men in general at the time of Haller were under the ban of the doctrines of George Ernst Stahl (1660-1734), a brilliant metaphysical philosopher, and unfortunately for science of his day, an influential writer and man of exceptional individual force. He assumed that all physical and chemical processes in the living creature, even the very simplest, were fundamentally different from those in the lifeless world, in that they were induced and controlled by a "sensitive soul," the "Anima Sensitiva." This conception is entirely different from that of the "reasonable soul" of Descartes, by which this philosopher meant to differentiate man from animals. Stahl's "Anima" reminds one more of the "*φύσις*" of Hippocrates, or the "Archæus" of Paracelsus and of van Helmont, for it is present in all that is living and disappears from it when death occurs. Stahl was the first "Vitalist" and his "Anima" was inseparable from the central nervous system. It is evident from this definition that an organ that could function when entirely separated from brain and cord was unthinkable to the medical world of Haller's day, when the doctrines of Stahl exerted a kind of tyranny over the opinions of physiologists. Now when the Bernese Aristotle with his then unassailable objective demonstrations and the force of his logic correctly proved the entire independence of the activity of the heart from the central nervous system—not only this, but even more, for he emphasized the irritability of the myocardium itself as the cause of the cardiac rhythmic activity;<sup>16</sup>—he dealt a killing blow from which the hypothesis of Stahl could not recover.

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<sup>16</sup> *Elementa*, Vol. I, p. 488.

As said before, Haller must be credited with the first correct and complete presentation of the mechanism of respiration, for there were other prominent anatomists, Hamberger (1697-1755) for one, who held that the lung contracted by its own inherent power, like a muscle, and that the pleural space between the lung and thoracic wall contained air. Haller succeeded in preparing the costal pleura in a living animal without injuring it in the least, so that the lung could be seen through it. He showed that the lung passively expanded, whilst it followed the receding thorax and descending diaphragm. His description of the diaphragm is anatomically perfect.<sup>17</sup>

It is regrettable that the chemistry of respiration was a "terra incognita" to him, who like many other thinkers of his time was held perplexed in the dark maze of Stahl's phlogiston theory. He knew of John Mayo's work on Respiration, and even cites it, but he failed to understand what Mayo meant by his "Nitro-Aereal" or "Ignec-Aereal" particles. The appreciative mind of to-day reading Mayo's ideas in the light of later progress by van Helmont, Lavoisier, etc., can understand that Mayo meant that the part of the atmosphere that was essential for burning was essential for all the chemical changes on which life depends and that the "Nitro-Aereal" particles of air are the oxygen of to-day. It is questionable whether any of Haller's contemporaries understood Mayo, or even whether this English apostle of physiology was understood in his own country. I do not think it correct to assert, as Sir Michael Foster does,<sup>18</sup> that Haller rejected the advances of the English school (Boyle, Hook, Lower, and Mayo). He gave them fair consideration; he did not accept them; neither did he clearly reject them. He was an agnostic for the time, as most conservative thinkers should be. One must not overlook the fact that these men expressed themselves largely in terms of their own invention concerning their views of respiratory gases, and that they were unavoidably vague, and were not in entire agreement. After

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<sup>17</sup> De diaphragmate. Göttingen, 1791.

<sup>18</sup> Loc. cit., 230.



[70] discussing all views known to him, Haller declines to accept the view that particles of air actually pass into the blood; but immediately thereafter warns the reader that his doubt concerning the theories of the English school "does not or should not lead to the conclusion that in breathing we derive nothing from the air."

Haller induced his disciple Rhodes<sup>19</sup> to write a dissertation on the iron content of the blood (Göttingen, 1753) and he attributed the red color of the blood to the iron.

The physiology of the larynx is excellently presented in his *Elementa*,<sup>20</sup> but he appears not to have known the function of the lateral cricoarytenoid muscles in opening the glottis.

#### CONTRIBUTION TO THE PHYSIOLOGY OF DIGESTION.

To the modern student of Haller's physiology it soon becomes apparent that the weakest points of Haller's work are where he comes in contact with purely chemical phenomena in the explanations of the processes of life, and this is not surprising, since the chemistry of today was practically unknown. It was not until after Haller's death that Scheele, contemporaneously with Priestley, discovered oxygen in 1786. I have already referred to the retarding effect of Stahl's phlogiston hypothesis, which impeded the development of chemistry fully as much as the delusion that the septum of the heart is perforated did retard the development of the physiology of the circulation of the blood.<sup>21</sup> Even Scheele was an ardent adherent of the phlogiston theory. It is quite pardonable, therefore, that Haller, who had no special training in chemistry and had not even been an apothecary, like some of the clinicians and chemists of his time, should have no comprehensive knowledge of the chemical progress taking [71] place during his life and which was giving birth to a new chemistry under the stimulus of Black, Mayo, and Priestley in England and Lavoisier in France.

This same defect in interpretation we find in Haller's pre-

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<sup>19</sup> Boretan, *Gesch. d. Physiol.* (Julius Pagel writes this name Rhodes) in Part I of Neuburger's and Pagel's *Gesch. d. Med.*

<sup>20</sup> Vol. III, p. 366.

<sup>21</sup> Hemmeter. *Johns Hopkins Hospital Bulletin*, 1905, XVI, 165.

sentation of the functions of the digestive organs, where we [71] find many erroneous conceptions; but his description of digestion is distinctly in advance of the time. The activity of the salivary glands as dependent upon nerve influence (irritation by smell or taste) is an idea that does not appeal to him, although he concedes a certain degree of irritability to the salivary glands. To him the saliva is neither alkaline nor acid, and he interprets its function to be merely a mechanical one to aid in the formation of the bolus and facilitate swallowing. He does not know its starch-digesting property, for ptyalin was not discovered until 1831 by Leuchs.

The glands of the stomach furnish only mucus according to Haller. The gastric juice is a kind of transudate from the arteries; it is neither alkaline nor acid, but neutral. Acid is not present in the stomach normally; if present at all it is derived from abnormal decompositions of the gastric contents. In the sixth volume of his *Elementa*, page 57, he looks with disfavor on the use of the word "ferment," to explain the action of the gastric juice, which is, according to him, much assisted by the grinding and mechanical effects of the movements of the stomach.

The various functions of the pancreas are not known to him. Though he speaks of neutralization (*Milderung*) as being one of them, he does not mean neutralization of the gastric juice but of the bile.

The bile he considers to be an especially effective secretion for digesting the fats, which he declares are immediately emulsified by it. It is according to him not an excretion but a secretion and this he attempts to demonstrate by the effects of excluding bile from the intestinal canal. It was still thought by many physiologists that bile was produced in the gall-bladder, but he was an opponent of this belief, as he knew that bile is produced in animals who have no gall-bladder. In this connection he emphasized the importance of comparative physiology. In connection with his doctrines concerning digestion, his discussion of the foods and diet of human beings are very interesting, but naturally imperfect in the light of our present knowledge.<sup>22</sup>

<sup>22</sup> *Elementa*, Vol. VI, pp. 188, 258.

- [71] His description of the structure and the gross functions of the kidneys is admirable, but the chapter on the urine (this being again a chemical subject) is in accordance with the deficient knowledge of those days.

CONTRIBUTIONS, VIEWS, AND EXPERIMENTS CONCERNING THE  
CENTRAL NERVOUS SYSTEM.

Haller's work on the brain and spinal cord will be better understood after his doctrine of irritability has been studied. In testing the irritability of the brain and its membranes he frequently went too far, because of the incompleteness of his methods and crudeness of his instruments. A part of his first brain studies were upon the cerebral pulsations. In 1750 the Dutch physician Schlichting had shown that the pulsatory movements of the brain were caused by the activity of the heart and the respiratory movements, but at the same time had been led to assume a kind of independent brain movement. The question was taken up by the Paris professor Lorry, 1725-1786, who disproved the theory of an independent movement of the brain, but at the same time held that the brain pulsations were pathological. Haller<sup>23</sup> attributed the brain pulsations to venous stagnation. In his experiments on the gray cortex of the brain, he was assisted by his pupils Zinn and Zimmermann. The physiological techniques of these experiments were very faulty viewed from our present standpoint. They made use of needles and sticks of wood saturated in acid, which were stuck into the gray matter. It is not surprising that they always obtained the same results, namely collapse of the animals, and convulsions—the well-known epileptic attacks when the cortex is stimulated too powerfully. He considered the gray cortex as devoid of sensibility and attributes positive sensibility only to the white medullary substance. Thus he is opposed to ideas of localization, the beginnings of which had already been made by other physiologists. He recognized that the cerebellum, by carefully conducted experiments, could not be proven to be an organ that is essential to life,—that is, not more so than the

<sup>23</sup> *Elementa*, Vol. IV.

cerebrum; but he conceded the great importance of the [71] medulla as a portion of the brain that was immediately essential to life. This concession was, however, forced from him by his brilliant pupil Zinn. Lorry had shown that the only locality in the whole central nervous system through which convulsions could be caused invariably—that is of course after clean and careful experimentation—was situated in the medulla oblongata. Isolated injury of this spot could cause death, according to Lorry, and Haller recognized this also. Another epoch-making discovery he confirmed without reservation: the discovery of the contralateral innervation, by the French physician, Pourfour du Petit (1664-1741). This brilliant observer accurately described the crossed paralysis which occurred in trephined animals whose cortex had been injured on one side, and then demonstrated the decussation of the pyramids. There had been some intimation that such a crossing of the motor fibers probably existed, for the ancients had already described autopsy findings in persons who had died of apoplexy which foreshadowed the great physiological discovery of Pourfour du Petit.

THE NEW CONCEPTION OF IRRITABILITY AS FIRST PRESENTED  
BY HALLER.

In presenting this new aspect of living matter as first conceived by Haller it will be necessary to review the opinions held on this same subject by physiologists prior to him. Sir Michael Foster says "And to call attention to the general view of Glisson's because this was the mother idea which led him to a special conception of the properties of muscular tissue, through which he anticipated modern teaching by nearly a hundred years. In his work on the liver, in discussing how [72] it comes about that the bile is discharged into the intestines at certain times only, namely, when it is wanted, he shows that the gall-bladder and biliary duct bring about a greater excretion when they are "irritated." And he argues that they cannot be irritated unless they possess the power of being irritated. This power of being irritated he proposes to denote by the term *irritability*. And he develops this view again in his work on the Stomach (De Ventriculo), published



[72] the year of his death, though wholly written as early as 1662, but laid aside in order that he might devote himself to his work "*De Natura*."

"Thus it is undoubtedly to Glisson that we owe the first introduction not only of the word but of the idea of irritability, which, revived by Haller, as we shall immediately see, in the next century became firmly established in physiology and has played an important part in the development both of physiological and pathological views. Haller used the word in its narrower sense as the property through which muscle responds by movement to an external stimulus; since then it has been extended to mean response in any way, not by movement or change of form only but by kind of change, chemical change, change of growth, and the like. And it is worthy of note that Glisson from the very first used the word in its widest sense, distinguishing the various ways in which irritability may be manifested and the various agents by which it may be called forth."

It was perhaps by reason of the fundamental and highly philosophical character of Glisson's conception that it did not meet with immediate recognition. The idea had to be put forth in the narrower form, which Haller gave it, in order to be understood by physiologists; but to continue to use a comparison of Sir Michael Foster's: "Glisson's irritability and his notable experiment were like Mayo's igneo-aereal spirit forgotten as the seventeenth century passed into the eighteenth. We have to wait until the latter century, when the truth was brought to light again by the sagacious Haller in his views of nervous action and its relation to muscular contraction."

From this narrative it is evident how the merits of an older investigator may be overlooked in the future development of a new discovery. Glisson was undoubtedly correct in the broader conception and application of the term irritability. Haller's inseparable connection with this discovery is, however, justified through the large number of objective demonstrations and experiments by which he succeeded in proving this new quality of living matter. To us of the twentieth century it might occasionally seem as if irritability had from time immemorial been one of the primordial

conceptions of natural philosophers; and yet this property [72] which at the present day appears as one of the most natural attributes of living matter was not even dreamt of before the days of Glisson nor understood before the days of Haller. The introduction of the idea into physiology constituted as great an innovation and brought about as many reforms and advances in physiology as did the conception and development of the new physical chemistry of our present day.

The most correct course to pursue in speaking of Haller's views concerning irritability will be to quote his own words in his *Elementa*: "There is widely present not only in the animal, but also in the vegetable kingdom, a contractile force by which the elements are brought nearer to each other. This not only seems to be the cause of cohesion in general, but is rendered manifest by the fact that a fiber drawn out lengthways when let go very soon returns to its previous length." This is more properly the elastic force. Besides this there is a contractile force by which the tissues dead or alive shrink when treated in various ways, when for instance they are heated. A contractile force of such a kind is present in almost all animal tissue, unless it be very soft and pulpy ones like brain, or very hard ones like bones and teeth. But there is in addition a special contractile force proper to muscles alone. "In a living animal or one only just dead there very frequently appears spontaneously in muscular tissue a swift contractile movement by which the ends of the muscle are alternately brought nearer to the middle belly and then again recede from it. And even when this contractile movement does not spontaneously appear, it may be excited if a stimulus, such as pricking, or pinching, or some chemical substance is applied."

"Many writers consider this living contractile force as identical with the dead one just described as belonging more or less to all tissues." This view Haller discusses and concludes, "That muscular fiber is the only one which is moved spontaneously in the living animal, or is brought by irritants from rest to movement," and that "the living contractile force must be held to be distinct from the dead contractile

[72] force, since the two agree neither in the laws which govern them, nor in their duration, nor in their seat."

This force he calls *Vis Insita*, the Inherent Force, and the tissues possessing it he calls after Glisson "irritable."

He then discusses whether this property of irritability is identical with that of feeling, and concludes that it is not. "There are many parts which feel, but which are not irritable, and in particular, a nerve, which is above everything sensitive, and yet possesses no contractile force except that common one found, as stated above, even in dead things.

"Wherefore this force since it is different from mere elasticity and from that dead contraction which is common to all fibers, seems to constitute a peculiar property, proper to the muscular fiber, and indeed to mark the character of that fiber, so that every muscular fiber is irritable, and on the other hand you may fairly call muscular fiber everything that is irritable. It is, however, a force of its own kind, different from every other power, and to be classed among the sources of production of motion, the ultimate cause of which is unknown. This same force is inherent in the fiber itself and not brought to it from without.

"I (by my experiments published first in 1739, and again in 1743) separated this irritable nature on the one hand from a mere dead force, and on the other from the nervous force and from the power of the soul. I shewed that the movement of the heart and the irritable nature of the intestines [73] depended on it alone. I confined it entirely to the muscular fiber, in which point the Batavian school does not agree with me, but they will I hope do so when they are willing to distinguish the contractile force common to all animal fiber from the irritable force proper to muscle alone. I also shewed that that force was something perpetually living, and that it often broke out into movement though no external stimulus such as could be recognized by us was acting. By a stimulus, however, it could at any time be called back from rest into action. In a movement produced through it I distinguished between the stimulus, which might be very slight, and the movement called forth by the stimulus, which might be very powerful."

"Some," says he, "have wished to call this force the vital [731] force, but this does not quite please me, since the force may for some little time survive the life of the body. Hence I prefer to call it the force inherent in or proper to muscle."

Further on he says: "Besides this force inherent in muscular fiber, another force is exercised in it, so far like the former that it alone has its seat in muscular fiber. But it is different from the inherent force inasmuch as it comes from without and is carried to the muscles from the brain by the nerves, it is the power by which muscles are called into action." This he calls the *Vis Nervosa*. "It too may survive the death of the body, and in cold-blooded animals is of the same constancy as the inherent force; so that in such an animal recently killed, in which no sensation or voluntary movement remains, a muscle, provided it be moist and whole, is thrown into convulsions when its nerve is irritated. And the same is true of warm-blooded animals." Haller reached these conclusions by countless experiments upon the animals, the results of which he reported to the Göttingen Scientific Society, under the title of "*De partibus corporis sentientibus et irritabilibus*."

In his *Elementa*, Vol. IV, page 532, he described exhaustively all older theories of muscle contraction and emphasizes that the nerve has no inherent contractility of its own, nor can it move actively in any way, as had been asserted before his time. He reports concerning all former conceptions of the nature of nerve function and declines to believe the electrical hypotheses that arose for the first time in those days, and appears more willing to accept a theory explaining nerve function by the flowing of an actual nerve spirit, not in a gelatinous substance as Borelli thought, but in actual tubes.

In observing the expressions of pain and the movements of defense in the animal during his experiments on irritability, he finds that the sensibility of the various organs depends upon their wealth of nerves. The muscles also possess sensibility, side by side with irritability. The tendons and joints, according to him, do not possess sensibility to a marked degree and the peritoneum very little sensibility. The incompleteness of his physiological technic brought it about that he



[73] frequently went too far, particularly with his experiments in stimulating the dura mater and pia mater, as well as the cerebral cortex.

#### A CHARACTER STUDY OF HALLER.

To discern the intellectual peculiarity and the inner character of all human beings that have achieved greatness is always a difficult problem. One of the principal features in our philosopher and naturalist is his astonishing pleasure in detail and the second most prominent trait is his unusual joy and power of observation. Biographers frequently speak of the secret of the individuality, and correctly so. It is a secret, but not because individuality is the work of forces which are more subtle and puzzling than other forces. The riddle consists in the abundance and complication of the many coacting forces into which we can very rarely gain exhaustive insight. According to Theodor Gompertz (*Griechische Denker*) we might distinguish two fundamental types of world sages. In one there is a preponderance of thirst for fullness of knowledge and an insatiable reception of ever new and manifold material of insight. In the second, the most prominent feature is the striving toward inner freedom from contradiction, toward unconditional mental consequentialness and consistency. Insatiable thirst for knowledge on the one hand, and the desire to have a mind free from contradictions, a so-called logical and orderly mind on the other hand, are not necessarily diametrically opposed to each other. The two represent evidently only differences of degree, but the difference is for that reason none the less real. For a critical study of the state of the inner mind of great human beings reveals the surprising fact that these two qualities are rarely present in one and the same individual. Thinkers like Descartes or Spinoza, who erect a homogeneous and uniform thought structure, stone for stone, idea upon idea, and two detail workers like Aristotle and Leibnitz, who are ceaselessly engaged in special investigations of every kind, represent two deviating varieties of a common genus; for the sake of argument we may designate those engaged in restless detail work, the encyclopedists. This human mind may try ever so hard in seeking strict limitation and definiteness of his thought struc-

ture, for clearness in the inner arrangement of his mind, yet [73] he will never be as successful as an equally versatile intellect that is not animated by so strong a desire for fullness of knowledge, and hence not equally distracted. Insatiable thirst for knowledge in the encyclopedist must, however, eventually bring about a tendency toward clearing up of his thoughts. Such a man will serve the requirements for the arrangement and the systematization of an enormous mass of knowledge. The encyclopedist will mediate upon and invent artifices and tricks controlling the material of thought. An example of this we have in the language of concepts of Leibnitz; or the encyclopedist will become a classifier and systematizer, and as a matter of fact we find that all great human beings with a comprehensive grasp of knowledge tend toward this achievement. Classification and systematization were the great intellectual feats of Aristotle and Humboldt. But strangely enough the best biographers of both of these do not concede that they accomplished research work of enduring excellence. Aristotle was not a research worker in the modern sense of the word; his interpretation of actual [74] facts is often wilful and controlled by preconceived opinions. His interpretations show the inexhaustible resources of a head rich in inventive power, rather than the severe training of a mind that conquers its intuition and bows under the hard yoke of facts.

In Haller, however, we find for once a human intellect eminently fitted to serve classification and systematization; he has an orderly, logical, or consequential mind, and an insatiable thirst for fullness of knowledge, but it is conceded by the most capable judges of the present day that he was a research worker "par excellence."

The life of Haller and his works put to shame the sixteenth aphorism of Heraclitus.

*πολυμαθία νόον ἔχειν οὐκ διδάσκει.*

(Too much knowledge does not give understanding or insight.)

His life rather reminds one as fitting to the celebrated aphorism of Hippocrates,

*"ὁ μὲν βίος βραχύς ἡ δὲ τέχνη μακρά."*

(Life is short, but art is long.)









# Biochemische Zeitschrift.

Herausgegeben von

E. Buchner-Berlin, P. Ehrlich-Frankfurt a. M., C. von Noorden-  
Wien, E. Salkowski-Berlin, N. Zuntz-Berlin

unter Mitwirkung von

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Redigiert von

C. Neuberg-Berlin.

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*Sonderabdruck aus 11. Band, 1., 2. u. 3. Heft.*

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John C. Hemmeter:

Die Wirkung der Totalexstirpation sämtlicher Speichel-  
drüsen auf die sekretorische Funktion des Magens beim  
Hunde.



Berlin.

Verlag von Julius Springer.  
1908.

# Die Biochemische Zeitschrift

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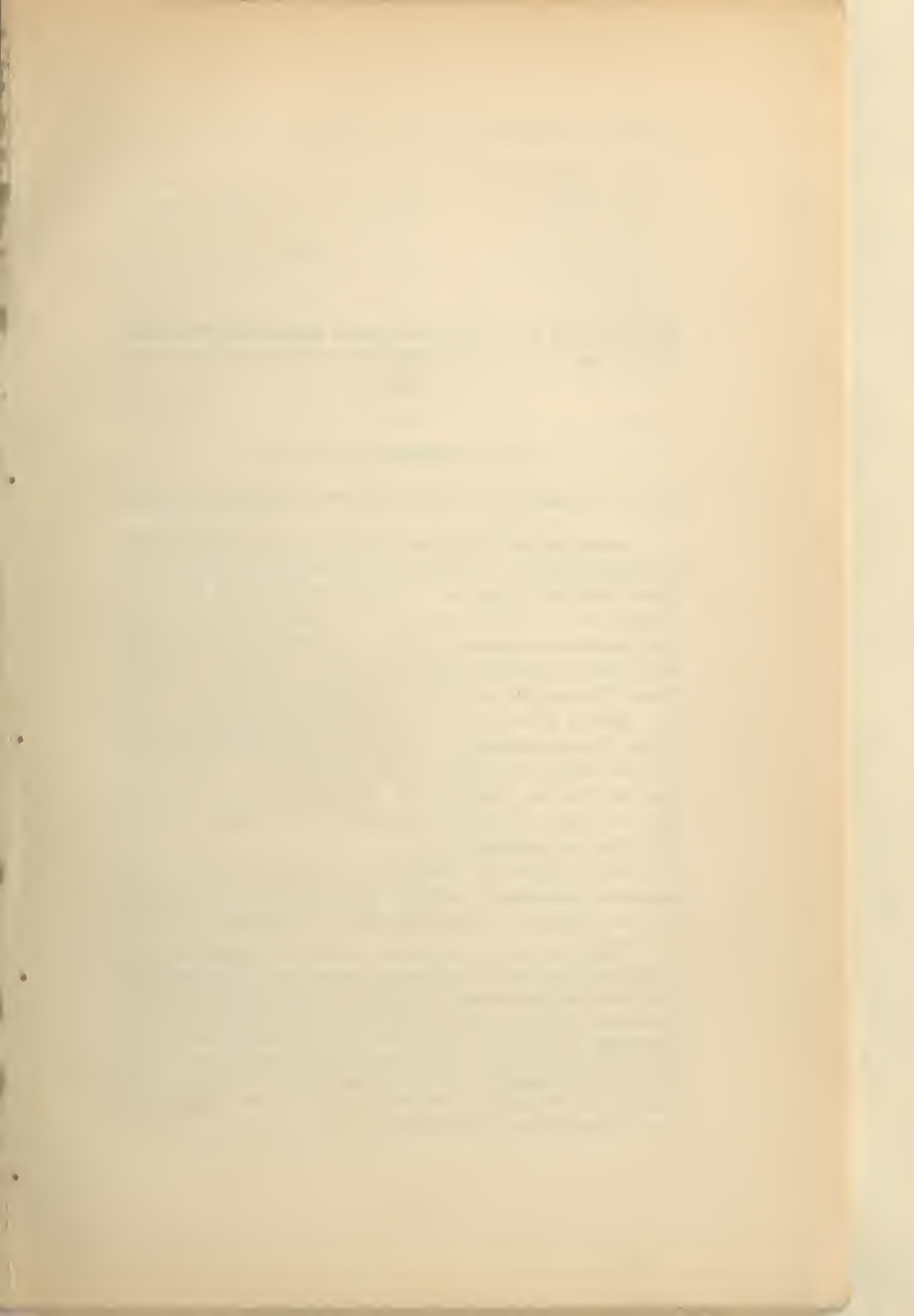
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**Verlagsbuchhandlung von Julius Springer**  
Berlin N. 24, Monbijouplatz 3.

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# Die Wirkung der Totalexstirpation sämtlicher Speicheldrüsen auf die sekretorische Funktion des Magens beim Hunde.

Von

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(Aus dem Physiologischen Institut der Universität Maryland, Baltimore.)

Aus klinischen Erfahrungen ist bekannt, daß Erkrankungen der Speicheldrüsen von verminderter Sekretion des Magens begleitet werden. Experimente, welche von Klinikern und Physiologen zu dem Zwecke ausgeführt wurden, die Sekretion der Speicheldrüsen auszuschalten oder zu zerstören, haben ergeben, daß solchen Versuchen gewöhnlich eine verringerte proteolytische Wirkung des secernierten Magensafts folgte.<sup>1)</sup>

Spätere Arbeiten über das interessante Verhältnis dieser beiden Organe zueinander wurden von E. Biernacki, Zeitschr. f. klin. Med., 21, Heft 1 und 2 veröffentlicht. Im „International Medical Magazine“ für August 1896 schrieb Julius Friedenwald eine Abhandlung über die Wichtigkeit des Speichels für die Magenverdauung.

Alle Forscher und Kliniker, die bisher über diese interessanten Beziehungen gearbeitet haben, suchten die Erklärung für den Einfluß des Speichels auf die Magensaftsekretion in

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<sup>1)</sup> Siehe Wright, „Der Speichel“, Ecksteins Handbibliothek des Auslandes, Wien 1844. Auch Bidder und Schmidt; „Die Verdauungssäfte und der Stoffwechsel“, 1852. Siehe auch George Sticker, „Wechselbeziehungen zwischen Speichel und Magensaft“, Volkmanns Sammlung klin. Vorträge d. inn. Med., Nr. 100, 297, S. 2699; derselbe Autor, Georg Sticker, hat noch eine Arbeit geschrieben, welche Licht wirft auf die Beziehungen zwischen Speicheldrüsen und Magen, in der Münch. med. Wochenschr. 1886, Nr. 32 und 33, betitelt „Hyperacidität und Hypersekretion des Magensaftes“.

der chemischen Zusammensetzung des Speichels selbst. Durch eine große Anzahl von Experimenten, die ich selbst an gesunden Studenten machte, überzeugte ich mich von der Richtigkeit der hauptsächlichlichen Schlüsse der vorhergenannten Forscher und Beobachter, d. h., daß die proteolytische Wirksamkeit entschieden stärker war, wenn Speichel den Probespeisen beigemischt war und wenn normales Kauen und Verspeichelung stattgefunden hatte, als wenn die Nahrung direkt durch eine Sonde in den Magen geführt worden war, und so der Speicheleintritt in den Magen verhindert war.

Daß diese durch das Fehlen des Speichels und Kauens verursachte Verminderung der Magenverdauung keine Folge des Verlusts an Ptyalin war, wurde durch Experimente an Hunden bewiesen, deren Speichel vorher als frei von Ptyalin befunden worden war. Bei zwei Hunden wurde die Speiseröhre durchgeschnitten und das obere und untere Ende dieser gespaltenen Röhre in die äußere Halshaut genäht.<sup>1)</sup> Auf diese Weise konnte man die Nahrung wieder zurück erhalten, die bereits vom Hunde gekaut und verspeichelt worden war. Zugleich erhielt man, wenn diesen Tieren eine einfache Magenfistel angelegt war, nach Scheinfütterung einen reinen und klaren Magensaft. Dieser Saft hatte im Durchschnitt dieselbe proteolytische und milchcoagulierende Kraft wie derjenige von Hunden mit einem künstlichen Magen. Man darf nicht vergessen, daß in jedem Falle der Saft von einer Magenschleimhaut gewonnen worden war, die mit der Nahrung nicht in wirkliche Berührung gekommen ist; denn selbst beim künstlichen Magen berührt die Nahrung nicht die secernierende Oberfläche. Es kann daher nicht der Einwand gemacht werden, daß die proteolytische Wirkung des gewonnenen Saftes durch im Speichel enthaltene peptogene Substanzen beeinflußt oder nicht beeinflußt worden war (oder daß die Nahrung mit Speichel vermischt war).

Wenn die Hunde gefüttert wurden, indem man ihnen Brot, Rindfleisch oder Milch direkt durch eine Sonde ohne Kauen oder Verspeicheln in den Magen führte, und die Nahrung dann wieder erhalten wurde, indem man sie entweder durch eine Magensonde ausheberte, wie es bei dem Probefrühstück geschieht,

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<sup>1)</sup> Nach Pawlow; Ergebnisse d. Physiol. 1, 1. Abt., S. 256.

oder eine einfache Magenfistel anlegte, so ergab sich, daß man die Sekretion eines Magensaftes von beträchtlich verringerter proteolytischer und milchcoagulierender Kraft verursacht hatte — verglichen mit dem Magensaft desselben Hundes nach normalem Kauen und Schlucken seiner Nahrung —, oder verglichen mit dem Magensaft derselben Hunde nach „Scheinfütterung“, — oder selbst verglichen mit dem aus einem künstlichen Magen erhaltenen Magensaft. Man muß die Tatsache nicht übersehen, daß der aus einer filtrierten Probemahlzeit gewonnene Magensaft nicht dieselbe proteolytische Kraft haben kann wie der reine Magensaft, den man auf eine der beschriebenen operativen Arten erhält, da einige der aktiven Bestandteile des Magensaftes in solche chemische Verbindungen mit der Nahrung eingehen, daß sie ihre physiologische Aktivität nicht mehr ausüben können. Daher ist es nicht logisch, den Magensaft aus filtrierter Probenahrung mit dem Magensaft aus einem künstlichen Magen zu vergleichen oder mit demjenigen mit einfacher Magenfistel, nachdem die Zufuhr von Nahrung in dieses Organ durch Speiseröhrendurchschneidung verhindert worden ist.

Im Laufe dieser experimentellen Versuche ergab sich nun, daß die verminderte Magenverdauung — nach Mahlzeiten, die nicht gekaut oder verspeichelt waren — nicht dem Mangel an Ptyalin zuzuschreiben war; denn es war erwiesen, daß bei einigen der Hunde der Speichel normalerweise frei von Ptyalin war.

In den vorangegangenen Experimenten an normalen Studenten waren wir schon zu dem Schlusse gekommen, daß dieselbe Verminderung der Magenverdauung nicht der chemischen Reaktion (Alkalinität) des Speichels zuzuschreiben war, da einige der Versuchspersonen regelmäßig neutralen Speichel aufwiesen; bei einigen war der Speichel sauer und bei anderen amphoter.

Bei immer neuen Experimenten und klinischen Beobachtungen tauchte der Gedanke auf, daß vielleicht der Einfluß der Speicheldrüsen auf die Sekretion des Magensaftes durch irgend etwas sich besonders in den Speicheldrüsen Bildendes hervorgerufen würde, d. h. durch eine von der Speichelsekretion vollständig getrennte und verschiedene Funktion.

Diese Frage konnte bei Hunden nur durch chemische



Analyse ihres Magensaftes geprüft werden, indem man eine quantitative Bestimmung seiner physiologischen Wirkungen vor und nach vollständiger Exstirpation der Speicheldrüsen anstrebte. Bei dem Versuche zur Lösung dieser experimentellen Frage waren es hauptsächlich drei Punkte, die sich aufdrängten.

Der erste war: Welche Wirkung hat die vollständige Entfernung der Speicheldrüsen auf die Sekretion des Magensaftes?

Der zweite: Wenn die Menge der Sekretion sowohl hinsichtlich der proteolytischen als der milchcoagulierende Kraft vermindert ist, d. h., wenn die Menge von HCl und Fermenten verringert würde, kann sie dann wieder entweder durch Verfütterung von Speichel drüsen oder von ihren Extrakten direkt mit der Nahrung oder durch Injektion von Extrakten der Speicheldrüsen in die Zirkulation zu ihrer Norm zurückgeführt werden?

Der dritte Punkt betrifft die Methode, mittels welcher der Magensaft gewonnen werden sollte. Soll er gewonnen werden:

a) durch Aushebern des Probefrühstücks durch eine Magensonde, b) durch einen künstlichen Magen, c) durch eine einfache Magenfistel?

Eine Gewinnung des Magensaftes nach der Spaltung der Speiseröhre durch „Scheinfütterung“ entsprach nicht unserem Zweck, da solche Tiere die Nahrung nicht mehr in der gewöhnlichen Weise schlucken können und das normale Kauen und Schlucken für das Studium gewisser aktueller Probleme wesentlich war.

Die Anlegung eines kleinen Magens nach Pawlow ist, meiner Erfahrung nach, immer eine sehr schwere Operation und bei persönlichen Erkundigungen in amerikanischen physiologischen Laboratorien habe ich gefunden, daß es anerkanntermaßen eine schwierige Sache ist, ein solches Tier über die Folgen einer derartigen Operation zur vollständigen Wiederherstellung zu bringen. Wenn jedoch die Operationen der Exstirpation der Speicheldrüsen schon vorangegangen sind, so wird die Operation des künstlichen Magens eine viel ernstere, und es gehen daran mehr Tiere zugrunde, als dieses ohne Entfernung der Speicheldrüsen der Fall gewesen wäre. Die Exstirpation der Speicheldrüsen hat durch mehrere Operationen zu erfolgen. Es hat sich als recht empfehlenswert herausgestellt, erst diejenigen auf der einen Seite zu entfernen, näm-



lich die Parotis [orbitalis, Submaxillaris und Sublingualis, und dann einen Monat bis zur vollständigen Wiederherstellung zu warten. Alsdann werden die Drüsen auf der anderen Seite in derselben Weise entfernt, und wieder drei bis vier Wochen zur vollständigen Heilung gewartet, ehe die Operation des künstlichen oder Pawlowschen Magens unternommen wird. Es ist natürlich absolut notwendig, die Magensaftsekretion vor und nach dem Entfernen der Speicheldrüsen zu prüfen, auch muß die Operation der Anlegung eines künstlichen Magens derjenigen der Exstirpation der Speicheldrüsen vorangehen, — im Falle der Magensaft auf diese Weise studiert werden soll. Die sog. Pawlow-Operation ist, meiner Erfahrung nach, eine so schwere, daß ich vor mehreren Jahren begann, eine neue operative Methode auszuarbeiten, die in kürzerer Zeit und mit weniger Nähen ausgeführt werden konnte. Ich glaube diese neue, vereinfachte operative Prozedur gefunden zu haben; sie ist in dem amerikanischen *Journal of Physiology* 17, 321 veröffentlicht: „An improved operative Method of Forming an experimental accessory (Pawlow) stomach in the dog.“

Hunde, die nach Pawlow operiert sind, zeigen häufig eine pathologisch vermehrte oder verminderte Sekretion, wenn man die Menge und die Wirkung der Sekretion mit derjenigen desselben Tieres bei identischen Probespeisen vergleicht in Fällen, wo der Saft durch „Scheinfütterung“ gewonnen ist, nachdem die Tiere mit einer einfachen Magenfistel versehen worden sind. Pawlow spricht von diesen pathologischen Phänomenen, erwähnt aber bloß Weigerung der Nahrungsaufnahme, Erbrechen und Lähmungserscheinungen. Er erwähnt nicht besonders irgend welche Veränderungen der proteolytischen Wirksamkeit des Sekretes nach der Operation.<sup>1)</sup>

Bei zweien meiner Tiere, an denen die Magensaftsekretion vor und nach der Pawlowschen Operation beobachtet wurde, war offenbar die Sekretion verändert; tatsächlich schwankten bei demselben Tiere die proteolytische und milchcoagulierende Kraft erheblich in den ersten zwei Wochen nach der Wiederherstellung. Pawlow nimmt an, daß die Störungen der Peristaltik und die Weigerung der Nahrungsaufnahme usw. reflek-

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<sup>1)</sup> *Ergebn. d. Physiol.* 1, 260.

torisch durch Beeinflussung der Nervenfasern verursacht werden, die sich in dem Gewebe, das den kleinen mit dem großen Magen verbindet, hinziehen. Es ist wahrscheinlich, daß die Sekretionsstörungen, die ich beschreibe, eine Folge derselben Nervenbeeinträchtigung sind. Diese sekretorischen Störungen hören zwei bis drei Wochen nach der Operation auf. Für unseren Zweck ist es wichtig, zu berücksichtigen, daß die Sekretion des kleineren Magens nicht immer ein richtiger Nachweis für die sekretorische Tätigkeit ist, die der Tiermagen unter normalen Bedingungen zu leisten vermag; z. B. konnte man bei einigen unserer Experimente mit Pawlowschen Hunden nach Exstirpation der Speicheldrüsen absolut keinen Magensaft aus dem kleinen Magen erhalten, wenn aber das Tier längere Zeit beobachtet wurde, kehrte die Magensaftsekretion allmählich bis zu einem gewissen Grade zurück, erreichte aber nie mehr ihre normale proteolytische oder milchcoagulierende Kraft.

Obleich der künstliche Magen unentbehrlich ist, wenn das Objekt reiner Magensaft — unvermischt mit Nahrung — sein soll, so ist dies für unsern Zweck nicht absolut wesentlich. Wenn wir einen Begriff von der proteolytischen und milchcoagulierenden Kraft des Magensaftes vor Exstirpation der Speicheldrüsen durch Abfluß der Nahrung mittels einer einfachen Magenfistel gewinnen können und dann später diesen selben Magensaft nach Entfernen der Speicheldrüsen beobachten können, so ist das alles, was für das Primärobjekt des Experiments erforderlich ist.

Diese Methode wurde von Tarulli und Pascucci 1901 angewandt, als sie den Einfluß der Milzexstirpation auf die Verdauungskraft des secernierten Magensafts beobachteten.<sup>1)</sup> Demgemäß werde ich in dieser Mitteilung nur über die an Hunden mit einfacher Magenfistel vor und nach Exstirpation sämtlicher Speicheldrüsen gemachten Beobachtungen berichten, und diejenigen, die an Hunden mit Pawlowschen Magen gemacht wurden, für eine spätere Veröffentlichung aufbewahren; denn sie sollten aus gewissen Gründen, die später anzugeben sind, in eine eigene Gruppe eingereiht werden.

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<sup>1)</sup> Physiologie des Menschen von Luigi Luciani, deutsche Übersetzung von Baglioni und Winterstein, 2, 151.

### Analytische Methoden.

In Anbetracht der Verwirrung, die noch besteht in bezug auf Wert, Genauigkeit und Anwendbarkeit der verschiedenen Methoden, die Menge freier und gebundener vom Magen secernierter HCl zu bestimmen<sup>1)</sup>, hielt ich mich an keine der Methoden, um die Menge freier und gebundener HCl festzustellen. Wenn der Magensaft dem Anschein nach freie HCl enthielt — nach Günzbergs Reaktion (Phloroglucin, Vanillin) oder nach der Resorcinprobe von Boas —, so wurde die Menge freier und gebundener HCl nach Hoffmann-Ostwald bestimmt, wie dies in H. J. Hamburgers bekanntem Werk „Osmotischer Druck und Ionenlehre“ 2, 499 beschrieben ist. Wir wandten auch Töpfers Methode an, sie immer ergänzend durch die Phloroglucin-Vanillinprobe. Die milchcoagulierende Kraft wurde beurteilt nach der Zeit, die erforderlich war, um in 5 ccm Milch mittels  $\frac{1}{2}$  ccm Magensaftfiltrats Coagulation zu verursachen. Die proteolytische Wirksamkeit wurde nach Mett gemessen und die Methode gewöhnlich durch die von Hammer-schlag kontrolliert<sup>2)</sup>, vorausgesetzt, daß genügend Magensaft gewonnen worden war, um beide Methoden auszuführen. Nierenstein und Schiff<sup>3)</sup> haben Metts Methode sehr wesentlich vervollkommenet, und ihre Abänderung kam zur Anwendung. In sehr zweifelhaften Fällen, wenn keine Wirkung auf Mettsche Röhrchen erfolgte, verwendeten wir nach Chittenden präpariertes Blutfibrin<sup>4)</sup>; aber wir können diese Experimente mit Fibrin außer acht lassen, denn, wenn alle Proben für freie und gebundene HCl negativ waren und keine Einwirkung auf die Mettschen Röhrchen erfolgt war, so war auch gewöhnlich keine merkliche proteolytische Wirkung bei Blutfibrin als Substrat zu verzeichnen.

Im fünften Jahrgang der Ergebnisse der Physiologie, S. 622 u. ff., ist die ganze moderne Literatur über Eiweißverdauung im Magen kritisch von Edgar Zunz bearbeitet worden. Wir beziehen uns auf die von ihm auf Seite 640 und 641 angeführten

<sup>1)</sup> Siehe Magensäure des Menschen von Martius und Lüttke, siehe auch Hemmeters Diseases of the Stomach, third edition.

<sup>2)</sup> Wiener klin. Rundschau 1895, Nr. 23.

<sup>3)</sup> Arch. f. Verdauungskrankheiten 8.

<sup>4)</sup> Americ. Journ. of Medical Sciences 3, 39.



Daten, um die Tatsache darzutun, daß die zur vollständigen Magenverdauung erforderliche Zeit je nach der Menge des verzehrten Eiweißes schwankt. Die Behauptung verschiedener Physiologen, es sei unwahrscheinlich, daß man freie HCl aus einem Hundemagen 2 bis  $2\frac{1}{2}$  Stunden nach Fütterung mit Fleisch erhalten kann, ist unzutreffend, denn dieses hängt vollkommen von der Menge und der Beschaffenheit des Fleisches ab. Einige der angegebenen Ziffern zeigen eine vollständige Verdauung von 100 g rohen Rindfleisches innerhalb von 2 Stunden, während 100 g gebratenes oder geschmortes Rindfleisch 3 bis 4 Stunden erforderten. Bei Fütterung gesunder Hunde mit 50 bis 100 g rohem Rindfleisch war es immer möglich, Reaktion auf freie HCl in  $2\frac{1}{2}$  Stunden zu erzielen.

Um den Einfluß der Speicheldrüsen auf die Magensaftsekretion oder die Wirkung der Exstirpation dieser Drüsen darzutun, wird es notwendig sein, die Experimente im Hinblick auf Beantwortung folgender vier verschiedener Punkte einzurichten:

1. Die normale Proteolyse- und Milch-Koagulationszeit nach bekannten Mahlzeiten von Brot, Fleisch und Milch:

- a) wenn der Chymus durch Ausheberung mittels der Magensonde gewonnen wird,
- b) wenn er mittels einer einfachen Magenfistel erhalten wird.

2. Proteolyse- und Milch-Koagulationszeit nach vollständiger Exstirpation sämtlicher Speicheldrüsen — bei denselben Tieren nach denselben Probemahlzeiten.

3. Proteolyse- und Milch-Koagulationszeit beim Füttern der Tiere mit Brot und Rindfleisch, das bereits von normalen Tieren mit unversehrten Speicheldrüsen gekaut und eingespeichelt worden ist. Dies ist notwendig, um die Frage zu beantworten, ob die Wirkung der Speicheldrüsenexstirpation auf die Magensaftsekretion, wenn überhaupt eine beobachtet wird, dem Mangel an Speichel zuzuschreiben ist oder nicht.

4. Proteolyse- und Milch-Koagulationszeit des Magensaftes eines speicheldrüsenlosen Hundes nach Injektion von SpeicheldrüSENSaft bei Tieren:

- a) mit unversehrten Vagi,



b) mit gespaltenen Vagi — rechter Vagus im Hals durchgeschnitten, linker Vagus subdiaphragmatikal.

Tabelle 1, Serie A zeigt die proteolytische Kraft und Milch-Coagulationszeit eines Brot-, Fleisch- und Milchsafte, gewonnen von drei Hunden vor der Entfernung der Speicheldrüsen. Serie B, Tabelle 2 gibt dieselben physiologischen Daten von Magensaftfiltraten nach mittels Magensonde vorgenommenen Probemahlzeiten. Tabelle C illustriert die Proteolyse- und Milch-Coagulationszeit der Hunde Nr. 1, 2 und 3 (derselben, auf die sich auch Tabelle 1, Serie A bezog), aber Serie C zeigt die Wirkung der Exstirpation der Speicheldrüsen. Beim Vergleich der physiologischen Wirkungen des Magensaftes der Hunde in den beiden Tabellen beobachtet man, daß beim Hund Nr. 1 in Serie A der Brotsaft eine proteolytische Kraft von 4,0 und 4,5 mm Mett ergab; aber nach Exstirpation der Speicheldrüsen wurde die proteolytische Kraft auf 0,5 und 0,8 mm Mett entsprechend reduziert. Alle Ziffern, die sowohl unter proteolytischer Kraft als unter Milch-Coagulationszeit angeführt sind, geben den Durchschnitt von 10 Untersuchungen wieder.

Wir kehren zu Hund 1, Serie A zurück; er zeigt eine Verminderung von 4 mm Mett bei normalen Speicheldrüsen auf 0,5 mm Mett, nachdem sämtliche Speicheldrüsen entfernt worden waren, ein Verlust von 3,5 mm Mett beim Brotsaft. Ähnlich war die Milch-Coagulationszeit bei diesem Hunde nur 2 Minuten und 30 Sekunden bei unversehrten Speicheldrüsen, er erforderte indes 3 Stunden und 10 Minuten, nachdem die Speicheldrüsen entfernt waren. Tabelle D zeigt die proteolytische und milchcoagulierende Wirkung von Brot, Fleisch und Milchsaft vor der Injektion von Speicheldrüsenextrakt, und dieselbe Tabelle enthält zum Vergleich die Erhöhung dieser physiologischen Tätigkeiten des Magensaftes desselben Hundes nach intravenöser Injektion von Speicheldrüsenextrakt. Die Tabellen D und E verzeichnen die Wirkungen intravenöser Injektion von Speicheldrüsenextrakt mit folgendem Unterschied: bei Tabelle D wurde der Chymus durch eine einfache Magen-fistel gewonnen, bei Tabelle E jedoch mittels einer Magensonde.

Bezüglich der vier Fragestellungen auf Seite 245 und 246

illustrieren die fünf angegebenen Tabellen die in den Nr. 1, 2 und 4 aufgeworfenen Fragen. Sie zeigen jedoch nicht die Wirkung der Zufuhr einer Nahrung, die bereits von normalen Tieren gekaut und eingespeichelt worden und von ihnen durch eine Ösophagusfistel gewonnen worden war. Dieses experimentelle Vorgehen war notwendig, um die Sicherheit zu gewinnen, ob die verringerte Magensaftsekretion nach Exstirpation der Speicheldrüsen dem Mangel an Speichel zuzuschreiben war oder nicht. Wenn die Magensaftsekretion wieder nach der Zufuhr von Nahrung eintrat, die von einem normalen Hunde gekaut und eingespeichelt worden war, so schien der Schluß gerechtfertigt, daß die verminderte Magensaftsekretion beim speicheldrüsenlosen Hunde dem Mangel an Speichel zuzuschreiben war und nicht dem Mangel einer inneren Sekretion der Speicheldrüsen.

Es ist wohl unnötig, noch eine Tabelle beizufügen, um die Wirkung der Ernährung mit bereits eingespeicherter Nahrung auf speicheldrüsenlose Hunde anzugeben; denn die Resultate dieser Versuche können in einem einzigen Satze zusammengefaßt werden. In keinem Falle, in dem die proteolytische Kraft und Milchcoagulation bei speicheldrüsenfreien Hunden entschieden verringert worden waren, konnten sie durch Fütterung mit bereits von normalen Hunden eingespeicherter Nahrung wieder erhöht werden.

Die intravenöse Injektion von Speicheldrüsenextrakt erwies sich als wirksam, um die verringerte proteolytische und milchcoagule Kraft wiederherzustellen, innerhalb einer Zeit, die je nach der Menge des injizierten Extraktes zwischen 6 und 10 Stunden schwankte; aber gewöhnlich konnte sie die physiologischen Fähigkeiten des Magensaftes nicht bis zum Normalstande wiederherstellen, der beobachtet worden war, ehe die Speicheldrüsen entfernt gewesen waren. So betrug beim Hund Nr. 1 die normale proteolytische Kraft vor Exstirpation der Speicheldrüsen 4,0 und 4,5 mm Mett. Sie fiel auf 0,5 und 0,8 mm Mett nach dem Entfernen der Speicheldrüsen, stieg aber wieder, nicht ganz bis zur Norm, [indem sie 3,0 und 2,5 mm nach Injektion von Speicheldrüsenextrakt erreichte. Diese Ziffern beziehen sich nur auf den Brotsaft des Hundes Nr. 1.

Bezüglich der Wirkung des Schnittes durch die Vagi

auf das Resultat intravenöser Injektionen von Speicheldrüsenextrakt zeigt unsere experimentelle Arbeit, daß bei speicheldrüsenlosen Hunden, die von der Vagioperation sich erholt hatten (rechter Vagus im Halse durchschnitten, linker Vagus subdiaphragmatical) die intravenöse Injektion von Speicheldrüsenextrakt noch die Kraft besitzt, die verminderte Magensaftsekretion vorübergehend wiederherzustellen, jedoch nicht bis zum normalen proteolytischen und Coagulationsstande.

Diese Experimente zeigen, daß die Wirkung der Injektion von Speicheldrüsenextrakt nicht durch Vermittlung von Vagusfasern, sondern direkt auf die Zellen der Pepsindrüsen ausgeübt wird.

#### Die psychische Sekretion des Magensaftes bei Hunden ohne Speicheldrüsen.

Bei speicheldrüsenlosen Hunden, denen eine einfache Magen fistel angelegt ist, kann die psychische Sekretion des Magensaftes ebenso wirksam hervorgebracht werden wie bei Hunden mit unversehrten Speicheldrüsen. Dies läßt vermuten, daß ein Teil des Magensaftes, der noch nach Entfernung der Speicheldrüsen secerniert wird, der Bildung durch eine psychische Sekretion zuzuschreiben ist, veranlaßt durch Eindrücke auf die Sinnesorgane des Hundes während er die Nahrung schmeckt, riecht und sieht. Da diese Eindrücke auf die Gesichts-, Geruchs-, Geschmacks- und sogar Gehörorgane während der normalen Fütterung der speicheldrüsenlosen Tiere unvermeidlich waren, so entstand die Frage, wieviel von der nach Exstirpation der Speicheldrüsen beobachteten Magensekretion dieser psychischen Sekretion zuzuschreiben ist? — Dies erforderte eine besondere Reihe von Experimenten, in denen die Tiere mittels einer Magen sonde gefüttert wurden, nachdem ihnen Augen, Ohren und Nasenlöcher zugebunden worden waren. Speisen, die direkt durch eine Magen sonde in den Magen eingeführt wurden und aus Brot, Fleisch und Milch bestanden, zeigten sich fähig, bei den speicheldrüsenlosen Hunden eine Magensaftsekretion hervorzubringen. In einigen Fällen wurden die Speisen, ohne Wissen des Hundes, durch eine Magen fistel eingeführt, und einmal hatte ich einen Hund mit einem künstlichen (Pawlowschen) Magen, bei dem die Scheidewand zwischen



dem größeren und den künstlich angelegten Teil des Magens derartig einriß, daß sie eine klappenartige Öffnung hinterließ, die es dem Beobachter ermöglichte, Nahrung durch den künstlichen Magen in den Hauptmagen des Tieres einzuführen. Diese Klappe wirkte jedoch derartig, daß Wasser vom Hunde in seinen Hauptmagen geschluckt werden konnte, und doch nichts von dem Wasser durch den künstlichen oder experimentellen Magen entwich. Bei diesem Tiere war es leicht, Nahrung einzuführen, ohne eine psychische Sekretion zu verursachen, und es ergab sich, daß bei speicheldrüsenlosen Hunden, bei denen psychische Sekretion erfolgreich verhindert wird, eine Magensaftsekretion nach gewissen Speisen eintritt. Diese Sekretion ist unzweifelhaft peptogenen Substanzen (den „Hormonen“ von Starling) zuzuschreiben, die in der Nahrung selbst enthalten sind, oder dem sogenannten Pylorus-„Sekretin“ oder Hormon von Edkins.<sup>1)</sup>

#### Der Mechanismus der Magensaftsekretion

ist ein komplizierter. Pawlow hat im Anschluß an die Arbeit von Bidder und Schmidt die Existenz einer reinen und einfachen psychischen Sekretion auf physischer Basis, auf sicheren, experimentellen Wegen, festgestellt.

Tarulli und Pascucci haben in Luigi Lucianis Laboratorium<sup>2)</sup> Beobachtungen gemacht, die das Vorhandensein peptogener Substanzen nachwiesen, die während der Zeit der Verdauung aus der Milz extrahiert werden können.

Die vorliegende Reihe von Experimenten spricht deutlich für das Vorhandensein eines Hormons, das fähig ist, die Magensaftsekretion anzuregen; es kommt in den Speicheldrüsen vor und wirkt auf dem Wege des Blutkreislaufes. Bei Beginn dieser Beobachtungen fand man, daß gelegentlich Tiere mit künstlichem Magen und exstirpierten Speicheldrüsen absolut keine Magensaftsekretion zeigten; und auf dieses Phänomen wurden irrige Schlüsse gebaut, die in einer vorläufigen Mitteilung dargelegt, und in Science, Oktober 11, 1907, S. 473, New-York veröffentlicht sind. Es wurde darin behauptet, daß bei Hunden mit künstlichem Magen die Entfernung der

<sup>1)</sup> Journ. of Physiol. 34, 133, 1906.

<sup>2)</sup> Luciani, Physiologie des Menschen 2, 151.



Speicheldrüsen endgültig jede Magensaftsekretion aufhebe. Dies wurde als richtig bei drei Hunden beobachtet, die in der beschriebenen Weise operiert wurden, aber bei zweien dieser Tiere, die noch sechs Monate nach der Operation erhalten wurden, bemerkte man eine allmähliche Wiederkehr der Magensaftsekretion. Das vollständige Versagen der Magensaftsekretion, das manchmal nach irgend einer schweren Operation am Tiere beobachtet wird, ist die Folge einer direkten Schädigung des sekretorischen Apparates, verursacht durch die Operation selbst, oder die Einwirkung auf die Nerven, oder auch durch die Nervenreflexwirkungen; denn Pawlow behauptet, daß eine nur wenige Minuten andauernde Reizung des Sciaticus einen vielständigen Stillstand der Magensaftsekretion verursachen kann.<sup>1)</sup> Es ist deshalb bei diesen Experimenten nötig, die Tiere lange zu beobachten und ihnen Zeit zur vollständigen Wiederherstellung zu lassen, ehe die chemische Untersuchung des Magensaftes unternommen werden kann. Im Gegensatz zu jenen Hunden, deren Magensaftsekretion unmittelbar nach einer Operation aufhört, haben wir gelegentlich ein Tier gefunden, dessen Magensaft nach Exstirpation der Speicheldrüsen weiter secerniert wurde. Wenn er auch nicht in normalen Mengen secerniert wurde, so war die Verminderung jedoch nicht derartig, wie wir sie durchschnittlich bei den anderen in den Tabellen verzeichneten Tieren finden. Wir sind der Ansicht, daß dieses Andauern der Magensaftsekretion einem abnormen Zustand des Drüsenapparates des Hundemagens vor Beginn der Operationen zuzuschreiben ist. Die pathologische Art der Sekretion, die in dieser Verbindung sehr verblüffend ist, besteht in Hyperacidität und Hypersekretion. Pawlow hat bereits einen Hund mit Hyperacidität beschrieben, und M. Pewsner<sup>2)</sup> schildert einen Hund, der an Hypersekretion litt. Die auffallendste Abnormität ist jedoch ein Zustand, den ich zuerst beschrieben und „Heterochylie“ benannt habe. Dies ist ein abwechselnder Zustand, einerseits von Magensaftsekretion, die sich durch ausgesprochenen Überschuß aller Saftbestandteile kundgibt, und andererseits

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<sup>1)</sup> Work of the Digestive Glands.

<sup>2)</sup> Diese Zeitschr. 2, 344.

völligen Versagens der Sekretion nach ein und denselben Probenspeisen. Daß dieser Zustand vorkommt, ist von J. Boas, Berlin, bestätigt worden.<sup>1)</sup> Alle derartigen Abnormitäten der Sekretion machen das Tier ungeeignet für diese Art von Untersuchungen.

### Verschiedenheiten in der peptogenen Kraft der Speicheldrüsenextrakte.

Bei Beginn dieser Versuche etwa vor 5 Jahren, beobachtete ich eine beträchtliche Verschiedenheit der peptogenen Kraft der aus Speicheldrüsen hergestellten Extrakte. Sie wurden damals in einer ähnlichen Weise präpariert, wie dies W. N. Bayliss und E. H. Starling in „Ergebnisse der Physiologie“, 5. Jahrgang, S. 672 angeben. Ich kann die Ursache der Verschiedenheiten in den physiologischen Wirkungen der Speicheldrüsenextrakte nicht erklären; aber man kann sie möglicherweise finden: a) in einer falschen Methode, den Extrakt zu bereiten, b) im nicht frischen Zustand der Drüsen zur Zeit der Extraktion, c) in der Herstellung des Extraktes aus Drüsen im Ruhezustand und nicht aus solchen, die gearbeitet haben. Kürzlich sind solche Extrakte von Dr. T. B. Aldrich, bei Parke, Davis & Co., Detroit, Michigan, für mich hergestellt worden.

### Methode der Präparierung der Drüsenextrakte.

Das Bindegewebe wurde so weit wie möglich entfernt, und die Drüsen durch Zermahlen mit Quarzsand in einen Brei verwandelt. Dieser Brei wurde dann bei einer Temperatur von 45 bis 50° C mit schwach essigsaurem Wasser ausgezogen. Die Temperatur wurde gelegentlich auf 80 oder 90° C gesteigert, und der Extrakt durch Papier filtriert. Da das Filtrat trübe war, wurde ein gleiches Volumen Alkohol von 94% hinzugefügt und diese angenähert 50%ige alkoholische Lösung wiederum filtriert; dann war das Filtrat vollkommen klar. Es wurde dann im Vakuum bis zu einem kleinen Volumen verdampft und zu der zurückbleibenden Lösung das dreifache Volumen 94%igen Alkohols hinzugefügt und dann filtriert. Das Filtrat wurde im Vakuum verdampft, und wenn der

<sup>1)</sup> Archiv f. Verdauungskrankheiten 8, 75.

Alkohol entfernt war, die entstandene Lösung filtriert und mit Chloreton versetzt.

### Andere Irrtumsquellen.

Drei Quellen eines möglichen Irrtums wurden geprüft, um das Verhältnis der Speicheldrüsen zur Speichelsekretion klarer zu stellen.

1. Haben andere Drüsenextrakte oder die Produkte von Ptyalin die gleiche Wirkung im Anwachsen der Magensaftsekretion? In diesem Zusammenhang fand man, daß Lymphdrüsenextrakt unwirksam war, aber Extrakt aus Milz, entnommen von Hunden auf der Höhe der Magenverdauung, eine ähnliche, aber weniger ausgesprochene Wirkung hatte, wenn er intravenös injiziert wurde. Die Einwirkungsprodukte von Ptyalin auf Kohlehydrate, Glucose, Dextrose, Maltose, übten keine solche Wirkung aus.

2. Kommen abnorme Speicheldrüsen bei Hunden vor? Zur Zeit als die erste Mitteilung über diesen Gegenstand veröffentlicht wurde, Juni 1907, waren wir nicht imstande, irgend welche anomalen Speicheldrüsen zu finden; aber am Schluß jener Reihe von Experimenten wurde zufällig bei einem in der Äthernarkose eingegangenen Hunde eine überzählige Speicheldrüse entdeckt. Diese Drüse hatte die Struktur der Parotis und wurde dort gefunden, wo gewöhnlich die Tonsille sitzt.

3. War die Magenschleimhaut bei den Hunden, deren Sekretion vermindert war, histologisch normal, oder war eine Entzündung hinzugekommen, welche die sekretorischen Zellen hätte zerstören können? Als Antwort hierauf habe ich mitzuteilen, daß bei einigen der Mägen nach dem Tode histologische Untersuchungen angestellt wurden und man keine Spur von Gastritis fand.

Es ist unsere Erfahrung gewesen, daß jedes lange Andauern einer normalen Magensaftsekretion bei Entfernung sämtlicher Speicheldrüsen einem der drei folgenden Faktoren zuzuschreiben war: a) daß die Lobulen der Parotisdrüsen nicht vollständig entfernt worden waren. Dies ist für die chirurgisch vollkommene Exstirpation die schwierigste Drüse; b) daß die psychische Sekretion nicht vollständig eliminiert worden war, die, wenn sie überhaupt einsetzt, in der Nahrung peptogene



Substanzen erzeugt, die fähig sind, die Bildung des Pylorus-Homons oder Sekretins, wie es zuerst von Edkins beschrieben, anzuregen; c) daß Abnormitäten der Sekretion vorhanden waren, ähnlich den im vorangegangenen beschriebenen.

#### Die Komplexität des Mechanismus der Magensaftsekretion.

Wenn die Sekretion irgend eines Drüsenorgans von so vielen mitwirkenden Faktoren abhängt, wie jenen, mit denen wir bei der Magensaftsekretion vertraut geworden sind, so ist es nicht logisch, zu erwarten, daß die Elimination eines jeden einzelnen dieser mitwirkenden Faktoren das vollständige Aufhören der Sekretion in jenem Organ hervorbringt. Wir wissen jetzt, daß der Mechanismus der Magensaftsekretion von drei, möglicherweise von vier Erregungsquellen abhängig ist: 1. die Vagus- oder die psychische Sekretion, 2. das Pylorus-Sekretin oder Hormon von Edkins, 3. die milzpeptogene Substanz oder das Hormon von Tarulli und Pascucci, und es ist der Zweck dieser Mitteilung, die Aufmerksamkeit auf eine ähnliche Substanz zu ziehen, die in den Speicheldrüsen gebildet und nicht mit dem Speichel abgesondert wird, sondern den Magen durch den Blutlauf erreicht und hier einen der Anreize für die Magensaftsekretion bildet. Um die Größe der erregenden Kraft eines jeden dieser vier Faktoren mit Genauigkeit zu demonstrieren, wäre es notwendig, die anderen drei zu eliminieren; z. B., um die ausschließliche Wirkung der Speicheldrüsen auf die Magensaftsekretion zu beweisen, müßte der Versuch gemacht werden, einen Hund zu ernähren: erstens nach einem Schnitt durch beide Vagi, um die psychische Sekretion zu eliminieren, zweitens nach operativer Entfernung des Pylorus-Endes vom Magen, um die Wirkung der Pylorus-Sekretion von Edkins zu eliminieren, und drittens nach Exstirpation der Milz.

Wenn nach diesen Operationen der Magensaft noch immer abgesondert würde, und [wenn nach Entfernen der Speicheldrüsen diese Sekretion vollständig nachließe, so würde der Einfluß der Speicheldrüsen auf die Erregung der Magensaftsekretion ohne Zweifel festgestellt sein; aber selbst wenn ein Tier glücklich alle diese schweren Operationen überstehen würde, bleibt es doch zweifelhaft, ob die Schlußfolgerung dann ein-



wandsfrei ist. Nach dem, was wir über die Empfindlichkeit des Magendrüsenapparates wissen, ist es höchstwahrscheinlich, daß das Tier eine Einbuße an der Sekretion durch die direkten und indirekten Einflüsse dieser verschiedenen Operationen aufweisen würde.

### Übersicht und hauptsächliche Schlußfolgerungen.

1. Bei Hunden mit einfacher Magenfistel bewirkt die Exstirpation sämtlicher Speicheldrüsen eine ausgesprochene Verminderung der Magensaftsekretion. Dies geht auch aus der Analyse der Probenahrung hervor, die durch Ausheberung von Tieren mit intaktem Magen gewonnen ist. Es ist notwendig, die psychische Sekretion zu verhindern, um das beschriebene Phänomen hervorzubringen.

2. Selbst bei Tieren mit intakten Vagi kann es zuweilen vorkommen, daß die Entfernung sämtlicher Speicheldrüsen eine entschiedene Abnahme der Magensaftsekretion verursacht. Es scheint sogar in diesen Fällen ein ursächliches Verhältnis zwischen dem Verlust der Speicheldrüsen und der verminderten proteolytischen und milchbildenden Fähigkeit des Magensaftes zu bestehen.

3. Bei speicheldrüsenlosen Hunden, bei denen die Magensaftsekretion erheblich vermindert worden ist, wird diese durch Verabfolgung einer Nahrung, die von anderen normalen Hunden gut gekaut und eingespeichelt worden ist, nicht wieder bis zur Norm hergestellt.

4. Wenn die Magensaftsekretion vermindert ist, kann eine vorübergehende Wiederherstellung durch intravenöse oder peritoneale Injektion von Extrakten erzielt werden, die aus den Speicheldrüsen normaler Hunde hergestellt worden sind.

5. Diese vorübergehende Wiederherstellung der Magensaftsekretion findet sogar statt, wenn der Magen vom Zentralnervensystem isoliert ist.

6. Die chemische Koordination der Magensaftsekretion wird durch Hormone bewirkt, die verschiedenen Ursprunges sind; einige sind in der Nahrung selbst enthalten (Schiff, Bayliss und Starling); andere stammen aus der Pylorus-schleimhaut (Edkins), wieder andere haben ihre Herkunft in der Milz (Luciani), und die vorliegenden Experimente

weisen auf das Vorhandensein eines Magensaftsekretion erregenden, in den Speicheldrüsen gebildeten „Hormons“ hin. Speicheldrüsenextrakt wirkt nicht anregend auf die Magensaftsekretion, wenn er mit der Nahrung eingegeben oder direkt in den Magen eingeführt wird. Im frischen Zustand zermahlen, verursachen Speicheldrüsen annähernd die gleiche Magensaftsekretion wie eine äquivalente Menge Rindfleisch.

Es ist möglich, daß diese verschiedenen chemischen Mechanismen verschiedene Wirkungen auf die Magensaftsekretion ausüben.

Es wird unsere Aufgabe in einer künftigen Arbeit sein, auszuführen, daß die rein nervöse oder psychische Sekretion und die Magensaftsekretion, die durch chemische Erregung oder Hormone aufrecht gehalten wird, obwohl sie beim normalen Tiere gleichzeitig wirksam sind, verschiedene Zwecke haben; die psychische Sekretion bewirkt die primäre Phase der Sekretion, d. h., die Befreiung von prozymogenen Elementen und von Säure schon in den Sekretionszellen, und die chemischen Mechanismen beherrschen die sekundäre Phase oder die Wiederherstellung des Cytoplasmas.

Bei früheren Beobachtungen über Exstirpation der Speicheldrüsen wurde der Tatsache, daß Tiere ohne Speicheldrüsen ziemlich gut leben und verdauen können, zu viel Bedeutung beigelegt. Bei dieser Behauptung können wir uns darauf berufen, daß Tiere auch ziemlich gut leben und verdauen können, wenn ihnen die Milz, ja selbst wenn ihnen der ganze Magen herausgeschnitten worden ist. Wie in vorstehendem gezeigt worden ist, schließt die Mitwirkung der Speicheldrüsen bei Bildung von Pepsin und Salzsäure die Möglichkeit nicht aus, daß Pepsin und Salzsäure auch bei Abwesenheit der Speicheldrüsen gebildet werden können. Es ist z. B. bewiesen worden, daß die Milz eine wichtige Rolle bei der Bildung von Trypsin aus dem entsprechenden Zymogen spielt.<sup>1)</sup> Es war schon von M. Schiff 1862 angenommen worden, daß die Milz auf der Höhe der Verdauung eine Substanz in das Blut absondert, die von dem Pancreas zur Bildung von Trypsin verwendet wird, und, obgleich seine Resultate skeptisch aufgenommen worden sind, so wurden sie später von Herzen, Cachet

<sup>1)</sup> Luciani, l. c. 78.

und Pachon bestätigt. Noch später erzielten F. Bellamy, Mendel und Rettger Ergebnisse, welche die Lehre von Schiff bestätigten; so steht es heute fest, daß die Milz bei der Bildung von Trypsin aktiv beteiligt ist; aber dessenungeachtet hat man gefunden, daß die Pankreasdrüse von Tieren, denen die Milz vollständig ausgeschnitten worden war, Trypsin enthält. Dieser Streit über die Beziehung der Milz zur Bildung von Trypsin ist lehrreich; er wirft auch ein Licht auf die Beziehung der Speicheldrüsen zum Magen. Die Tatsache, daß Pepsin und HCl bei Abwesenheit der Speicheldrüsen gebildet werden können, darf nicht als Beweis dafür gelten, daß die Speicheldrüsen keine peptogene Substanz bilden. Die vorstehend beschriebenen Experimente sprechen zur Genüge für die Lehre, daß die Speicheldrüsen einen Einfluß auf die Bildung der Magensaftsekretion ausüben.

Es ist meine Pflicht, zum Schluß den Chirurgen der Universität Maryland für ihren geduldigen Beistand bei all diesen Operationen zu danken, die ohne eine vollkommene operative Technik nicht erfolgreich hätten durchgeführt werden können. Mein Dank gilt hauptsächlich den Professoren Frank Martin, St. Clair Spruill und J. Mason Hundley.

Tabelle A.

Durchschnitt von 10 Analysen von einem Hunde mit einfacher Magen-fistel. Analysen des Magensaftes vor Entfernung der Speicheldrüsen.

Nr. des Tieres	Menge des Magen-saftes, der zur Milch ge-setzt wurde ccm	Brotsaft		Fleischsaft		Milchsaft	
		Ver-dauungs-vermögen nach Mett	Koagu-lations-zeit	Ver-dauungs-vermögen nach Mett	Koagu-lations-zeit	Ver-dauungs-vermögen nach Mett	Koagu-lations-zeit
		mm	Min. Sek.	mm	Min. Sek.	mm	Min. Sek.
1	0,5	4,0	2 30	3,0	3 5	2,5	25 —
1	0,5	4,5	3 —	2,6	3 5	1,9	28 —
2	0,4	5,2	2 20	3,05	4 8	2,45	24 —
2	0,3	5,0	2 20	3,6	2 5	2,6	30 40
3	0,55	4,8	2 35	3,8	3 8	2,2	22 —
3	0,55	4,5	2 30	4,2	3 5	2,5	20 30

Diese Zahlen sind mit filtriertem Magensaft erhalten; sie weisen daher nicht die Verdauungskraft auf, die man gewöhnlich bei künstlichem oder Pawlowschen Magen erhält.

Durchschnittliche Acidität des Brotsaftes: 45 in 1000 } titrimetrisch  
 „ „ „ Milchsafte: 48 in 1000 } als HCl  
 „ „ „ Fleischsaftes: 50 in 1000 } berechnet.



Tabelle B.

Analyse des Verdauungs- und Milchkoagulierungsvermögens eines filtrierten Magensaftes, der nach einer Probemahlzeit von Brot, Fleisch und Milch ausgehebert war. Das Gewicht der Hunde schwankte zwischen 7 und 8 kg. — Die zur Verdauung von 100 g rohem Fleisch erforderliche Zeit betrug im Durchschnitt 7—8 Stunden. Nach 8 Stunden wurde der Magen leer befunden. Die Speicheldrüsen waren vorhanden.

Nr. des Tieres	Menge des Magensaftes, der zur Milch gesetzt wurde ccm	Brotsaft		Fleischsaft		Milchsaft	
		Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.	Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.	Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.
4	0,5	5,0	3 —	3,5	4 —	2,45	20 —
4	0,4	5,2	3 30	3,6	4 30	2,4	25 —
5	0,5	4,5	3 40	3,6	4 6	2,6	22 —
5	0,4	4,8	3 30	3,8	3 50	2,6	22 30
6	0,4	4,6	2 30	4,—	3 8	1,9	24 —
6	0,5	4,8	2 40	3,8	4 —	2,0	25 —

Durchschnittliche Acidität des Brotsaftes: 42 in 1000 } titrimetrisch  
 „ „ „ Milchsafte: 46 in 1000 } als HCl  
 „ „ „ Fleischsaftes: 52 in 1000 } berechnet.

Tabelle C.

Magensaft vom Hund mit einfacher Magenfistel nach Entfernung der Speicheldrüsen. Analysen des Verdauungs- und Milchkoagulierungsvermögens von filtriertem Magensaft, der nach einer Probemahlzeit aus Brot, Fleisch und Milch gewonnen war.

Nr. des Tieres	Menge des Magensaftes, der zur Milch gesetzt wurde ccm	Brotsaft		Fleischsaft		Milchsaft	
		Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.	Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.	Verdauungsvermögen nach Mett mm	Koagulationszeit Min. Sek.
1	0,5	0,5	3 10	0,5	3 50	0,3	4 20
1	0,6	0,8	2 50	0,6	2 50	0,5	3 50
2	0,6	1,0	2 25	0,8	3 10	0,5	4 30
2	0,5	1,0	2 25	0,9	3 5	0,3	4 35
3	0,4	0,8	3 —	0,5	3 10	0,4	4 50
3	0,5	0,8	3 30	0,5	3 5	0,5	4 35



Tabelle D.

Speicheldrüsenlose Hunde. Verdauungs- und Milchkongulationsvermögen nach Entfernung der Speicheldrüsen; einfache Magenfistel (s. Tabelle C. 1).

Vor Injektion des Speicheldrüsenextraktes.

Prüfung des Saftes 1 bis 2 Stunden nach Verabfolgung von 150 g rohem Fleisch oder 150 g Brot oder 150—200 ccm Milch.  
Intakte Vagi.

Nach Injektion von Speicheldrüsenextrakt.

Nr. des Hundes	Brotsaft		Fleischsaft		Milchsaft		Menge des in die Femoralis inji- zierten Speichel- drüsenextraktes	Zeit der Injektion des Extraktes vornittags	Zeit 1,30 nachm. Brotsaft		Zeit 1,30 nachm. Fleischsaft		Zeit 1,30 nachm. Milchsaft	
	Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.			Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- dauungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.
1	0,5	3 10	0,5	3 50	0,3	4 20	5 ccm in 5 ccm $\frac{1}{1}$ -Salz- lösung	10,00	3,0	5	2,0	10 5	1,2	1
1	0,8	2 50	0,5	2 50	0,5	3 50	do.	10,15	2,5	6	1,5	10 5	0,8	45
2	1,0	2 25	0,8	3 10	0,5	4 30	do.	9,45	3,5	4 30	1,8	12	0,9	40
2	1,0	2 25	0,9	3 5	0,3	4 35	do.	10,00	3,5	4 30	3,0	11 5	1,0	1 5
3	0,8	3	0,5	3 10	0,4	4 50	do.	10,00	3,2	5 10	3,2	8	1,5	1 5
3	0,8	3 30	0,5	3 5	0,5	4 35	do.	10,10	3,4	6 20	2,5	9 5	0,8	40

Diese Daten zeigen in ausgesprochener Weise die zeitweilige Wiederherstellung der Verdauungskraft und des Labungsvermögens unter dem Einflusse intravenös injizierten Speicheldrüsenextraktes. Jedoch war dieser Auszug nicht instande, die in den verschiedenen früheren Versuchen zutage getretene normale Wirksamkeit des Magensaftes wiederherzustellen.

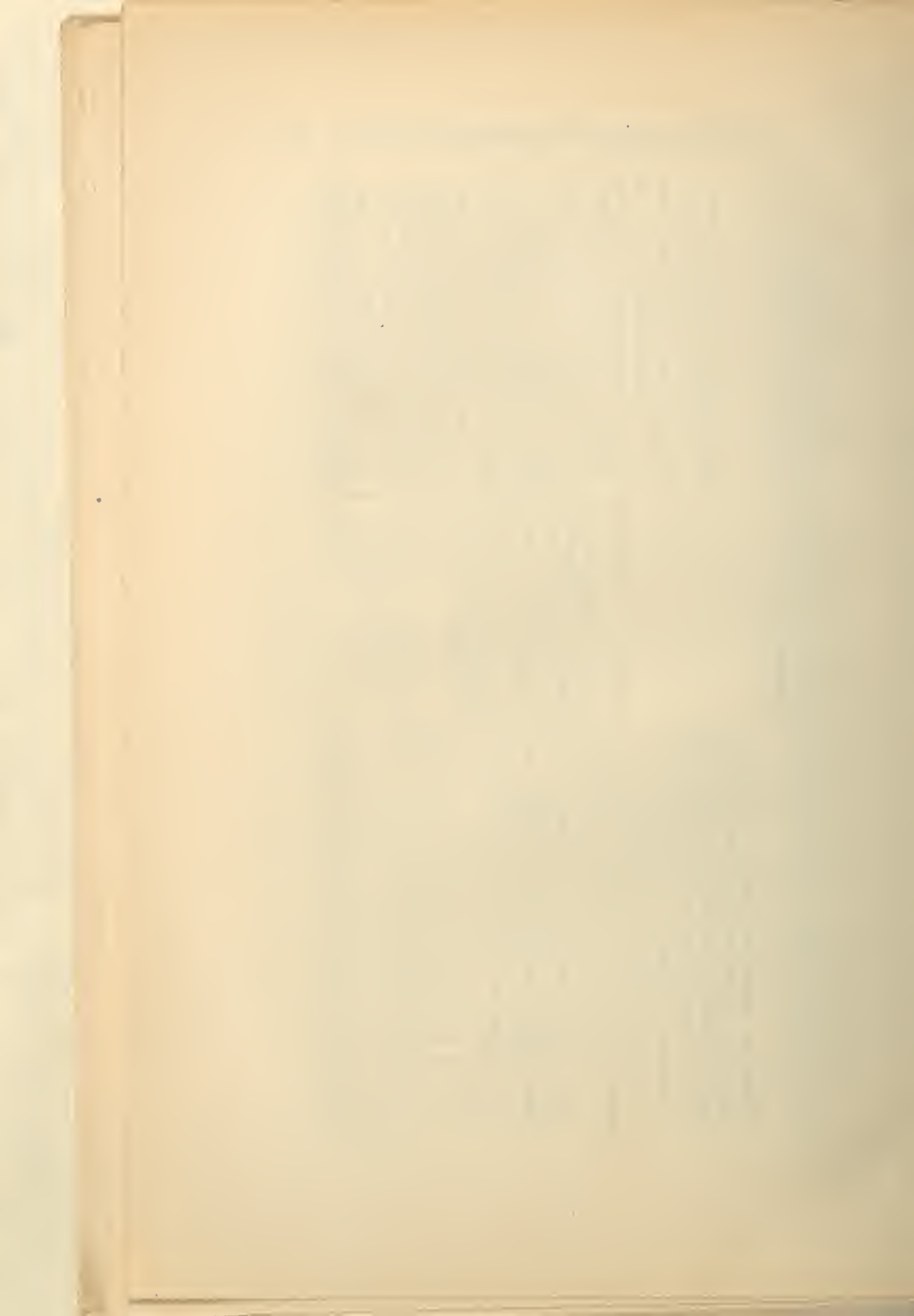
Tabelle E.

Wirkung der intravenösen Injektion von Speicheldrüsenextrakt auf die speicheldrüsenlosen Hunde der Serie B. Probenahmezeit aus 200 g Brot, 100 g Fleisch und 150 cem Milch. Der Saft wurde durch Aushebern gewonnen. Exstirpation der Speicheldrüsen.  
Vor Injektion des Speicheldrüsenextraktes:

Prüfung des Saftes nach einer Verdauungszeit von 1—2 Stunden.

Nach intravenöser Injektion von Speicheldrüsenextrakt:

Nr. des Hundes	Brottsaft		Fleischsaft		Milchsaft		Zeit der Injektion des Extraktes vormittags	Menge des in die Femoralis inji- zierten Speichel- drüsenextraktes	Brottsaft		Fleischsaft		Milchsaft	
	Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.			Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.	Ver- daunungs- ver- mögen nach Mett mm	Koagu- lations- zeit M. S.
4	1	2 30	0,8	3 40	—	4 5	11,10	10 cem in 10 cem $\frac{1}{1}$ -Salzlösung	2,5	10	2,2	15 5	1,5	45
5	0,8	2 30	0,5	2 55	0,2	4 10	10,45	do.	2	10 3	2,5	12 4	1,4	52
5	0,8	2 25	0,6	2 55	—	3 60	10,45	do.	2,4	12 5	2,0	12 2	0,9	52
8	1,5	3 10	0,9	3 10	0,1?	4 10	11,00	do.	3	15 5	1,5	20	1,8	56
9	1,0	3 20	0,9	3 20	—	4 20	11,00	do.	2,5	10 3	1,6	20 2	1,9	58
4	0,8	2 30	0,6	3 40	—	4 6	11,00	do.	2,4	10	2,3	15 2	1,5	1st 2m.



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REPLY AND EXPLANATION TO RECENT CRITICISM  
OF MY EXPERIMENTAL STUDY ON EFFECTS OF  
EXTIRPATION OF THE SALIVARY GLANDS  
ON THE GASTRIC SECRETION

By JOHN C. HEMMETER

Reprinted from the Proceedings of the Society for Experimental Biology and Medicine,  
1909, vi, pp. 33-44.



**Thirty first meeting.**

*Rockefeller Institute for Medical Research. December 16, 1908.  
President Lee in the chair.*

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**Reply and explanation to recent criticism of my experimental  
study on effects of extirpation of the salivary glands  
on the gastric secretion.**

By **JOHN C. HEMMETER.** (By invitation.)

*[From the Physiologic Laboratory of the University of Maryland,  
Baltimore.]*

It is not always a congenial task to have to reply to a criticism of one's experimental work. To many a conservative thinker, the policy contained in a remark attributed to Ludwig under a similar circumstance, "Schweigen ist gold," may appeal as more expedient. But yet, the dignified silence may be interpreted, by the one who has advanced the criticism and even by the research worker and general student of physiology, as a tacit approval to the fault finding — in other words, as signifying that the criticism was deserved and the work criticised defective. I find myself in this embarrassing position with regard to an article published in the "Proceedings of the Society for Experimental Biology and Medicine, 1908, v, pp. 114-117," New York, by Dr. A. S. Loevenhart and Dr. D. R. Hooker, entitled: "Note on the supposed presence of a gastric hormon in the salivary glands."

Although the physiology and pathology of digestion has been my life work, yet, as one of the results of many years of laboratory teaching and training, I am loathe to insist dogmatically on any of my opinions and am ready at any moment to be corrected and to advance another step in the attainment of truth. ("Experientia fallax, Experimenta mendax.")<sup>1</sup>

Especially welcome are such corrections when they emanate from such an esteemed friend and talented worker as Dr. Loeven-

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<sup>1</sup> But rather than dwell upon the moral side of scientific controversy I prefer to refer to Sir Thomas Browne's "Religio medici," 1904 edition, p. 98.



hart. The original worker whose results are criticised has the right, however, to demand that his special point of inquiry ("Fragestellung") and all the methods of experimentation, operative, physiologic and chemic, shall be conscientiously repeated on, at least, an equal number of the same kind of animals, successfully nursed through the identical operative procedures. He has a right to demand a scrupulous regard for detail, and for all the finer distinctions made in his application of methods, some of which may have required years for their perfection in his hands and those of his associates.

Let us investigate whether my friend, Dr. Loevenhart, has fulfilled these indispensable, fundamental conditions that should precede destructive criticism.

I sought to ascertain the effect of salivary gland extract in dogs deprived of all four pairs of salivary glands, whose gastric juice had been carefully studied before any operation of removing the glands was undertaken. Sometimes the removal had no very marked effect; but in those dogs in which it did, I tried to ascertain whether the depressed gastric secretion could be restored or not by salivary gland extract. I tried to study the effect on a secretion already abnormally depressed in three series of dogs — thoroughly recovered from the operation, allowing ten days to two weeks, at least, for recovery.

Dr. Loevenhart starts with normal dogs, as he supposes, and expects to raise the gastric secretion qualitatively and quantitatively *above* the normal. He seeks the effect of salivary gland extract in raising a supposedly normal gastric secretion to a higher acidity and proteolysis — an entirely different problem from mine.

I have never published anything on the effect of salivary gland extract on the normal gastric secretion of dogs. It is not asserted that this extract can raise the gastric secretion *above normal*, but only that it may, under certain conditions, partially restore a gastric secretion that is depressed *below* normal. Dr. Loevenhart is attempting to change a normal secretion to an abnormal (higher) one. I studied the effect in restoring an abnormal secretion to a normal one.

When there are four different procedures for obtaining gastric juice on the same dog within thirty minutes, and the jugular vein

exposed, a cannula inserted and submaxillary extract injected intravenously, it must not be overlooked that, with every additional interference, the animal becomes more and more disturbed and that this seriously influences his gastric secretion. The chemico-physical and the neuro-physical processes of secretion are thoroughly upset unless a long time for recovery is given. This is shown in Dr. Loevenhart's results, page 4 of his reprint, in which the total acidity and free HCl and the proteolytic power became less and less in specimens *A*, *B* and *C*; only when the psychic secretion was aroused, granting that this was not a delayed effect of injection sal. gl. extr. specimen *D*, was there any notable proteolysis without addition of acid. The notes of the beginning of experimentation on this dog bear the date of April 6, and the qualitative studies bear the date of April 8 — not near time enough to permit dog No. 2 to entirely recover.

To expect salivary gland extract to raise the gastric secretion qualitatively and quantitatively above what is the regular standard for the average dog is to expect something abnormal — for an unusually abundant and unusually active gastric juice is logically as abnormal as one that is unusually diminished or inactive.

1. What Dr. Loevenhart presumes is that the salivary gland extract should change a normal gastric juice to an abnormal one (from the regular amount to an unusually high amount and activity).

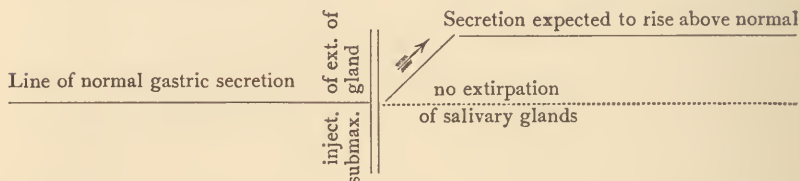
2. What I attempted to ascertain was whether or not an abnormal gastric juice could be restored to the normal (from diminished and weakened secretion to the normal). The "Fragestellung" is not the same, in fact, it is highly digressing.

Dr. Loevenhart observed only two animals. Nowhere does he give the date of operations, nor state the time that elapsed between the operation and first day of experimentation, nor the amount of proteolysis in millimeters of Mett tubes. Both animals were abnormal. The first dog, No. 1, he admits had distemper and was feverish, was thin and would not eat. The first observations are dated November 11, 1907, and this animal died within 48 hours.

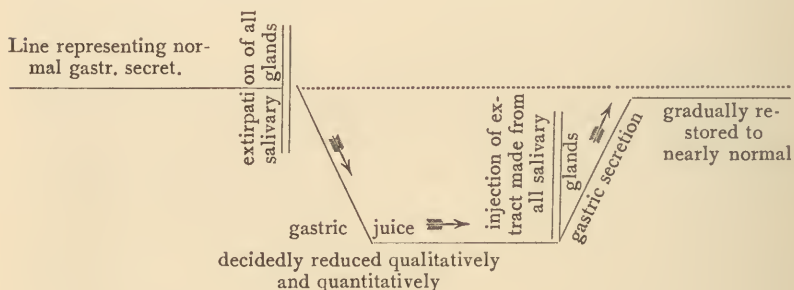
All of our results were gained from dogs that lived for three to six months and then had to be killed in most cases because we

had no room or facilities for keeping them during the summer vacation — excepting the series of the summer of 1907 when I kept four dogs at our country home.

What Dr. Loevenhart aimed at



What Dr. Hemmeter attempted to ascertain.



Dog No. 2 of Dr. Loevenhart was also abnormal. This is evident from the feeble proteolysis as indicated by Mett tubes (in Dr. Loevenhart's article they are called "Metz" tubes) and the low acidity, and Dr. Loevenhart gravely states that the fluid gained by catheterization, 8.6 c.c., specimen *A*, contained *much dark mucus* (blood? and mucus). Mucus in a fasting dog's stomach is one of the most reliable indications of gastritis. Dog No. 2 had a diseased stomach also.

We made our salivary extract from maceration of all four pairs of canine salivary glands, even the orbital — and it is all important that this extract should be made only from salivary glands that have been functionally active immediately before their excision (the dog must be made to chew bread and then rapidly etherized). I have worked with extracts of inactive glands, but so far have

refrained from publishing anything concerning their effects or non-effect. In not a single instance, has the operative plan and technique used by us, nor the physiologic routine of preparing the glands by functional work, nor the chemic discipline of ascertaining the proteolytic activity been punctiliously carried out by Doctors Loevenhart and Hooker.

Both of the animals had diseased stomachs. In neither were the salivary glands extirpated. The entire plan of experimentation and aspect of physiologic inquiry is so fundamentally different from mine, that comparison of their work with ours is not logical, and any deductions from their work as used to interpret our results are unfortunately misapplied.

It is only fair that the work of an experimenter should be judged from his most recent publication, in this case that which appeared in the *Biochemische Zeitschrift* (Hamburger Festschrift, Band xi, p. 238), the only complete report published by me.

The short notice by which Drs. Loevenhart and Hooker judged our work was nothing but a preliminary report, and contained, as such reports occasionally do, some inaccuracies which I have taken the privilege to correct in the article published in the *Biochem. Zeitschr.*, *l. c.* ("Die Wirkung der Total Extirpation Sämtlicher Speicheldrüsen auf die Sekretorische Funktion des Magens beim Hunde"). Even in this article the printer has allowed some wrong figures to slip into the headings of tables C, D and F, pp. 257, 258 and 259, for which I am in no way responsible, but which do not injure the main argument, especially as the editors of the *Biochem. Zeitschr.* politely corrected them in a subsequent *Berichtigung*.

In Dr. Loevenhart's experiment on April 8, submaxillary extract was injected into dog No. 2 at about 3.10 to 3.15 P. M., the gastric juice of twenty minutes later showed a free HCl of 0.20 (titration with  $n/20$  NaOH) but the proteolytic power with addition of acid is declared to be "*good*." But at 3.30 the stomach of the same dog was catheterized and specimen *A* obtained after the dog was allowed to smell meat for ten minutes. This specimen *A* was the most active that Loevenhart obtained. It came 35 minutes after the submaxillary extract was injected. Question is: Would not this active juice have been secreted even without



the efforts to cause a psychic secretion, for the salivary extract in my experience has a latent period in which it produces no very marked secretion? After that period it may come; that is, a pronounced secretion may come, even thirty minutes after injection of salivary extract and even if there has been no chance for psychic secretion. Pawlow, *l. c.*, p. 70, states that in all cases the latent period after the vagus stimulation of gastric secretion may be from 15 minutes to one hour, and even more.

Hitherto we have known the term "*latent period of secretion*" only in connection with the stimulation of a nerve going to gland or muscle. We are not so familiar with the use of the term "latent period" in connection with the chemical stimulation of a gland. A moment's reflection will bring the thought nearer to us that even after nerve stimulation, pure and simple, chemical events must transpire in the gland cells which require a certain time for their elaboration. Now, if the stimulation is purely chemical, and not through a nerve, the same or similar chemical events must precede the actual outpouring of secretion. We are still ignorant of the processes that occur during the "latent period," but recent work indicates that they are partially electrical and partially of a chemical nature. We must also consider that the immediate effect of a chemical stimulation, like the immediate effect of a nerve stimulation, may be inhibited.

There are so many side influences of a physical, nervous and chemical nature which control the phenomenon of the "latent period" that its exact nature and what transpires during it, is still a matter of speculation.

It may, at first sight, seem paradoxical that the latent period of secretion after sham feeding in dogs is stated by Pawlow to be only 5 to 10-15 minutes, and the latent period after vagus stimulation 15 minutes to one hour — for in both instances the stimulation is transmitted by one and the same nerve to the identical synapses in the gland cells. Pawlow explains this, p. 71, *l. c.*, by his belief that in artificial stimulation of the vagus, the stomach receives the excitatory as well as inhibitive impulses, and the latter check secretion.

How can we conceive of inhibitive processes to explain a long latent period of secretion, when chemical substances (for example,

salivary gland extracts) are injected intravenously? By an analogous experimental reasoning, we have learned (Pawlow, *l. c.*) that it is impossible to imitate the influence and action which the vagus exerts during normal life while digestion is going on for our laboratory methods are far too coarse and the complexity of fibers in this magnificent highway of nerve tracks too intricate for us to single out individually functioning secretory fibers.

We are not much better off when we attempt to imitate the chemistry of the internal secretion of glands, for only in a single instance has a hormon been isolated in a state that reveals its exact chemic structure.

The chemic messengers are bodies of definite chemic structure which are released with unerring exactness from their producing organs; but when we manufacture an organ extract, it is, of course, possible that we may seize the hormon (if I may still use the term); but unavoidably we must extract the entire tissue of the organ and as a result obtain extracts, which contain materials that stimulate, but also materials that may inhibit secretion. This occasional inhibitive effect of salivary gland extract on gastric secretion has brought to mind two ideas: either that I am not dealing with a hormon or stimulator at all, or that there may be two kinds of chemic correlation, one that stimulates and the other that inhibits. The conception which sees an antagonistic, as well as a synergistic, correlation brought about by chemic messengers is at least as rational, when applied to the physiologic correlation of organs by means of chemic substances communicated to them by means of the circulation, as when applied to the correlation of organs by means of nerve elements. This relation of organs by means of reciprocal (antagonistic or synergistic) action of nerves is not new to physiologists, and has been brought home to us in a most impressive manner by Meltzer, not to mention Ch. S. Sherrington, New York, 1907. All of this is still hypothesis; but this hypothesis has been given color (1) by the seemingly paradoxical effects of (*a*) such a pure substance as adrenalin, which does not always cause constriction of vessels (only when they are severed from the nerve centers) but sometimes may cause dilatation, when in normal animals a certain vascular area is intact in connection

with its nerve centers,<sup>1</sup> and of ( $\delta$ ) gland extracts, which sometimes raise blood pressure and often lower it (sometimes after a slight previous rise), and (2) by the contradictory effects of some salivary gland extracts on gastric secretion. All of this doubt will continue so long as we are compelled to deal with a complex mixture of various substances in gland extracts and not with one pure substance of known composition.

To this consideration belongs, also, the antagonistic phenomena reported by Lilienfeld, Morowitz and Delezenne as occurring in blood coagulation (positive and negative phase of coagulation). This is explained by Lilienfeld and also by Delezenne by the isolation from blood plates and leucocytes of two substances, one of which they term "*leuconuclein*" which favors coagulation, and the other, "*histon*," which retards coagulation. Before the isolation of these two substances the phenomenon of the positive and negative phase during blood coagulation appeared paradoxical, and the idea of a **latent period of coagulation** might have come to many an experimenter. Just so with the latent period after chemical stimulation of the glands; it may be due to inhibitive substances in the gland extracts used, and it is possible that this delay in bringing about the effect after chemical stimulation of the gastric glands, may disappear with a clearer knowledge of the chemistry of the gland extracts, and a more accurate method of preparing them.

Besides the latent period of secretion, we must consider the neutralization of the first acid secreted by the mucus present in the stomach. Pawlow ("Arbeit. d. Verdauungsdrüsen," *l. c.*, p. 39) calls attention to what he emphasizes as "Factum," namely, "*Even with a normal stomach and with a pure gastric juice 25 per cent. of its acidity can be lost through neutralization by mucus.*" How much more must this neutralization take place in a stomach that, as Loevenhart states, gave "*much dark mucus.*" The very efforts of catheterization increases the mucus formation, and after the submaxillary gland extract was injected, if it had any stimulating effect at all (I am not prepared to state whether it had or not) this much is sure, the mucus had to be neutralized before

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<sup>1</sup> This latter effect of adrenalin is not a purely chemical effect but a mixed effect of nerve and chemical phenomena. One and the same chemically pure substance cannot be claimed to contain both stimulating and inhibitive substances.

there could be free HCl. The extract was injected at 3.20 on April 10; at 3.25 P. M. the gastric juice was drawn by catheterization (8.8 c.c., specimen C). No free HCl was in it, but six minutes after the injection of salivary extract the dog was shown meat, and ten minutes after that there was a fourth catheterization (the fourth in 30 minutes). This 5.3 c.c. was active juice and Loevenhart and Hooker attribute it to psychic secretion.

Considering the latent period of secretion and the time for neutralization by mucus, it is reasonable to inquire whether or not the injection of extract had a feeble but delayed influence, although Loevenhart and Hooker used only submaxillary extract and not that of all four pairs of glands, and did not prepare it in the manner I did.

Concerning the inflammation (gastritis) in the stomachs of their dogs, I can very readily appreciate the difficulty, for I had been thwarted and misled by diseased canine stomachs for almost a year before we gradually learned to recognize, avoid and treat them.

Evidences like these, naturally suggest that such experiments cannot be successfully carried out in a few months. I was not aware of Dr. Loevenhart's criticism, until November 14, 1908. That there are salivary extracts that have no peptogenic effects whatever, and others that are variable, I have already stated in my article in the *Biochemische Zeitschr.*, Vol. xi, p. 251 ("Verschiedenheiten in d. peptogenen Kraft d. Speicheldrüsen Extrakten").

Then again, the complexity of the mechanism of gastric secretion in dogs is such (*Biochem. Zeitschr.*, l. c., p. 253) that the initial depression caused by extirpation of the salivary glands probably may be gradually replaced by special efforts of the remaining sources of stimulation to the gastric glandular apparatus.

This problem is far too deep and complicated to have years of laborious experimentation set aside by a casual testing of two sick dogs, as to whether a saline extract of the inactive submaxillary gland alone can cause a secretion of gastric juice in animals not deprived of their salivary glands.

That there may be defects in my work I am willing to accept as a possibility, because a general knowledge of the history of physiology reveals the status that the first results of similar ex-



perimental work are only in most exceptional instances without defects or errors.

Such a defect in the connexus of cause and effect has recently been brought to my knowledge and, today, makes it debatable whether the name "hormon" is correctly applied by myself to the stimulating quality of one gland extract upon the secretion of another set of glands. The definition and conception of the hormon allows a rather wide application, it is true, but it seems to me it ought to be restricted to substances whose chemical structure is at least approximately known and that have one predominant characteristic or specific effect on other glands, in which effect they cannot be replaced by extracts from other organs or tissues. This is not the case with the salivary extracts, for, as we can learn (*Biochem. Zeitschr.*, Vol. xi, p. 253), extracts of the pyloric mucosa and of the spleen (Luciani) act in a similar manner in stimulating gastric secretion.

Concerning the pepsinogenous effect of the spleen on the gastric secretion, I refer to the work of Tarulli and Pascucci, executed in Luciani's laboratory and described in the latter's splendid work, "Physiologie des Menschen," translated into German by Baglioni and Winterstein, Vol. ii, pp. 151 and 152. On page 153 it will be seen that the extract must be made from an *active* spleen, as Luciani says "a spleen that is hyperemic and swollen," which means, taken from a dog during the height of the digestive period. Extracts of spleen taken during the period of functional rest had no pepsinogenous effect; but the meaning of Luciani and his pupils above mentioned is unmistakable. A chemical substance is formed in the spleen during its activity which, when brought into the circulation, is absorbed by the gastric glands and is capable of augmenting the quantity of the secreted pepsin. Additional emphasis is given in these experiments to the fact that the extract should only be made from a functionally active gland.

Whatever may be the final outcome of investigations concerning the chemical nature of the hormones, Bayliss and Starling consider that they were originally accidental by-products of the activity peculiar and proper to the organ which has produced them. Thereafter the next step in the development of a correlation is the acquisition of a sensitiveness or a responsiveness to the hormones

in any remote organ ("Die Chemische Koordination der Funktionen des Körpers," *Ergebnisse der Physiologie*, Jahrgang v, p. 670). The only word to which I could take exception in this explanation of Bayliss and Starling is the word "accidental" ("Zufällige" Nebenprodukte). I should like to enlarge this conception when applying it to the digestive tract, and state that the various segments of the digestive tube are correlated and coordinated by a sensitiveness not *only to accidental products*, but to the regular by-products which are known to accompany the formation of the specific products of the organs of digestion.

An infirmity in the experimental logic, suggestive of a metabolic by-product produced in the salivary glands during activity which might be regarded as a chemical messenger to the secretory apparatus of the stomach, might be found in the occasional failure to produce total loss of gastric secretion after the salivary glands are removed. In other words, we should expect to find invariable "*Ausfalls-Erscheinungen*," phenomena of lapse or total deficiency of gastric secretion. That these do not occur after the salivary glands are extirpated with that regularity that is necessary to justify the use of the term "*hormon*," is at least partially explained by the existence of several other sources wherefrom the secretory apparatus of the stomach may receive its stimulations; these other sources have been sufficiently considered in the preceding and in the *Biochemische Zeitschrift*, Vol. xi, p. 253.

I do not wish to be understood as asserting that an extract of the inactive submaxillary gland alone can have an effect in raising the amount and proteolytic activity of gastric juice, but only, that, if it possibly could exert such an effect, not sufficient time was allowed after the injection in Dr. Loevenhart's experiments to adequately test this point of inquiry.

If there is anything of importance that has revealed itself to us since the publication in the *Biochemische Zeitschrift*, Vol. xi, p. 238, it has come through experimental study of the occasional long latent period after injection of some salivary extracts and not after others. This has suggested the existence of chemic substances which inhibit or check gastric secretion. These substances, if they exist as definite chemical bodies, must be more abundant in resting, than in functionally active, salivary glands.

There is nothing contradictory in the idea that one and the same gland cell in one segment of the digestive tract may contain two kinds of chemical messengers for the succeeding segment of the digestive apparatus. One kind stimulates secretion in the following segment and a second kind inhibits or arrests it.

Starling ("Recent Advances in the Physiology of Digestion," p. 90) speaks only of *hormones* (from *ορμω*, to excite, arouse or stimulate). But on reflection it must be evident that for the normal regulation of life processes, it may, under certain conditions, be equally important that any process of secretion or vascular tonus should be capable of inhibition by chemical messengers. Two such diagonally opposed chemical substances which are concerned in coagulation have been isolated from lymphocytes by Lilienfeld and Delezenne, one of which *leuconuclein* favors coagulation and a second *histon* which inhibits it. The *leuconuclein* corresponds to the *hormones* but the *histon* is an inhibitor. For such chemic bodies — physiologic arresters like *histon* — I would suggest the name *koliones* from the Greek *κωλύω*, to inhibit, to prevent, arrest or check.







## CHOLELITHIASIS: GALL-STONE DISEASE.

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THE principal factor in the formation of gall-stone is a catarrh of the biliary-ducts and gall-bladder, which is traceable in the majority of cases to an infection of the gall-bladder by micro-organisms. Stagnations in the flow of bile favor the development of this catarrh; but there is a second factor, which leads to the formation of gall-stones, to which little reference is made and to which the writer first called attention. It consists mainly of pathological alterations in the chemical composition of the bile. At the bottom of all this is an abnormal intermediate metabolism of the liver. To this view we are inclined because at many operations for gall-stone the gall-bladder itself, as well as the stone, the bile, and the various gall-ducts, were found to be free from bacteria; all cultures were negative.

Naturally it has been asserted that there may be bacteria which require such a culture medium as cannot be imitated outside of the living tissues of the body, and that these may cause gall-stone or inflammation of the biliary apparatus. This is a very far-fetched hypothesis, for there is no doubt that the only bacteria which are here concerned are those which originate from the intestine, and for all the more important intestinal bacteria there has been no difficulty of finding culture media.<sup>1</sup>

In speaking of the direct etiology we must consider everything which could produce stagnation of the bile-flow. Among these we must consider compressing clothing, insufficient bodily exercise, dislocation or compression of the bile-ducts by tumors, cicatrices. Among the causes which are little recognized I wish to call attention to one of which I have convinced myself repeatedly at autopsies; that is, enteroptosis, and gastropptosis especially. The displacement of the stomach may cause traction upon the hepato-duodenal ligament. This I have frequently seen at abdominal sections undertaken for gall-stone. Another cause is dislocated or floating kidney. Then, there seems to me to be a form of atony of the musculature of the gall-bladder, which in some way is dependent upon the traction caused by dislocated abdominal viscera in enteroptosis. The tugging upon the nerves

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<sup>1</sup> See Hemmeter, Diseases of the Intestines, Vol. I, article on Bacteria.

may also have an effect in this form of atony of the gall-bladder. The greater frequency of these etiological factors in the female sex explains the observation that gall-stones occur three to five times more frequently in women than in men. They also occur more frequently in old age. Prior to the thirtieth year only two to three per cent., and after the sixtieth year, twenty-five per cent. of the observed gall-stone cases occur.

It is of great importance to bear in mind the great rôle which certain infectious diseases play in the causation of cholelithiasis. As a rule these agents first cause a cholangitis and cholecystitis, and thereafter the injured mucous membranes of these parts produce altered secretions, and have lessened resistance to the micro-organisms that have invaded these pastures. One-third of my gall-stone cases had a previous history of typhoid fever, and I am inclined to look upon this infection as a very serious cause of gall-stones.

The size of the gall-stones varies from that of a sand grain to that of a hen's egg and larger. Their number may vary from a single one to a thousand. The form is very manifold; they may be round, oval, pear shape, mulberry shape, polygonal. Facetted stones arise by the friction of several concretions which are pressed against each other whilst they are still in a rather soft state. They may be of any color, white, yellow, gray, green, brown, even black; this color depends upon the external stratum of the stone, and need not necessarily represent the color of the interior. Most gall-stones consist of a hard stratified shell containing a soft interior. Generally there is a small hollow space in the center of this interior if it happens to be a perfectly dry stone.

They are mainly composed of bilirubin calcium, 15 to 30 per cent., and cholesterin, 60 to 80 per cent. There may be also a small amount of calcium carbonate, traces of copper and iron, also remnants of disintegrated epithelia and mucus. The pure cholesterin stones, which are white or yellowish, sometimes even transparent, are rare; the calcium carbonate stones are very rare. The material for the formation of the stone is furnished by detached and disintegrated epithelia.

The direct cause of the stone formation, then, is a catarrhal inflammation of the biliary apparatus, due mainly to micro-organisms, but which, in my opinion, can also be due to a pathologic metabolism of the liver. The stones at first consist of soft masses, which become coated with a thin shell. The continued growth is produced by concentric layers of cholesterin and bilirubin calcium on the outside, but at the same time there may be a progressive infiltration of the hollow space in the center with cholesterin.

The stones are most frequently found in a free state in the gall-bladder; they are very rarely adherent or encapsulated. The gall-bladder is always the seat of a cholecystitis which is partially the cause and partially the result of the gall-stone. Frequently the walls of the gall-bladder are thickened and contracted; the muscular and mucous layers are atrophic. I have seen the walls of a hypoplastic gall-bladder so tightly contracted around a stone as large as a pigeon's egg that it could only be cut away with considerable difficulty. The gall-bladder is rarely dilated. The bile which is contained in the

bladder is abnormally rich in mucus and disintegrating epithelial cells. Stones that occur in the cystic and common gall-duct originate in the gall-bladder, but can grow farther in the duct. A most frequent seat for the stones to become lodged in the ducts is the diverticulum of Vater, just in front of the orifice of the common gall-duct. Stones which lodge here and close up the orifice may produce a damming back of the bile into the pancreatic duct and eventually lead to inflammation of the pancreas and consequent fat necrosis. The gall-ducts may become enormously dilated in consequence of stagnation, caused by a stone. It has been observed that small stones, composed of bilirubin calcium, occur in the intra-hepatic bile-channels, and this when the gall-bladder and gall-ducts are normal. Evidently these tiny stones are due to faulty metabolism in the liver itself, and this to my mind constitutes one of the important evidences of the theory that there is a form of cholelithiasis which does not depend upon bacterial infection.

Gall-stones have been found in about one-tenth of all autopsies reported from European and American hospitals. Although this is an extraordinary frequency, it is interesting that the mere presence of gall-stones in the majority of cases causes no symptoms.

When symptoms do occur they are at first very indefinite, general distress and slight pains in the region of the liver, digestive disturbances, and slight icterus, are among the first symptoms and signs; but their dependence upon gall-stones is not always recognized in time. It is very rare that one is able to palpate the gall-bladder in individuals with thin abdominal wall, and it is still rarer that the actual observance of a passed stone in the stool permits the diagnosis in the absence of any preceding symptoms. I should, however, emphasize the following syndrome: If a person who has had an infectious colitis or dysentery or typhoid fever frequently complains of gastralgia two hours or three hours after meals, the clinician should exhaust his diagnostic resourcefulness to ascertain the existence or non-existence of gall-stone.

Characteristic disturbances occur only, then, when a stone has left the gall-bladder and entered the ducts, or after the presence of gall-stones has led to infections and inflammations of the duct. This condition gives rise to the so-called gall-stone colic. Thereby the stone may be evacuated into the intestine, and eventually pass out of the body; but rarely do all the stones pass out in this manner. We may distinguish the condition of the patient during the attack of gall-stone colic, and secondly, an irregular course of the cholelithiasis.

The direct and immediate cause of the colic is but little understood. It has been supposed that the stones already existing in the gall-bladder may be forced into the duct by concussions of jolting of the body, by a fall, by strong compression of the abdominal muscles, by vomiting, by operations on the other abdominal organs, by the act of labor, by cold, and by dietetic errors. The typical attack is generally preceded by discomfort, nausea, and a slight chill; but the pain may also start without any premonition whatever and continue in aggravated paroxysms until it becomes intolerable. But



even in the intervals a dull, boring soreness is always complained of in the center of the liver. From here the pain may radiate to the shoulder, epigastrium, spine, even into the legs. Sensitive patients may become unconscious or pass into a convulsion or delirium; vomiting is a frequent accompaniment. In about one half of these cases there is a pronounced chill followed by an elevation of the body temperature, which has been called the "reflex fever," but which is more correctly to be interpreted as the index of an infection of the biliary passages.

Enlargements of the gall-bladder only occur in one third of the cases, and is a consequence of the cholecystitis. Jaundice is an important indication for the interpretation of this colic, but in my experience it was absent in fifty-five per cent. of all cases of genuine gall-stone colic. The icterus may be observable in the conjunctivæ after twelve hours, and bile pigments may be present in the urine. There may be icterus without mechanical obstruction of the common gall-duct; this is an inflammatory stagnation caused by the invasion of the bile-passages by bacteria; but there may also be icterus due to functional disturbances in the liver cells due to general infection originating from the gall-duct. The duration of this jaundice is very variable; it rarely exceeds the regular attack of colic more than several days.

Even in intense icterus the stools are not always free from bile. If the fæces are sifted through a stool sieve it is sometimes possible to find the stone; but this is not the rule. It is possible that a stone has actually passed and that it has become disintegrated in the intestinal canal. During an attack of colic it would be an error to assume that a stone has always passed the common gall-duct or the cystic duct, for the pain may be caused by the acute cholecystitis; or the stone may have dropped back into the gall-bladder. The use of the stool sieve will be referred to later on.

After a typical attack of colic they cease after several hours as a rule, sometimes, however, only to be resumed with renewed severity; thus an attack may be protracted for several days. If a stone has actually passed then the cessation of pain is abrupt. The pains may be very slight in other cases, or entirely absent in still others, and the passages of a stone only evidenced by transient swelling and sensitiveness of the liver to pressure, or by a very slight icterus. The intensity of the pain is by no means proportionate to the size of the stone; for the irritability and smoothness of the biliary passages, the hardness, shape and configuration of the stone determine the pain. It is a singular thing that the largest stones pass with little pain or no pain at all, namely, by formation of fistula. I possess a gall-stone which was vomited by one of my patients who rarely complained of abdominal distress. The stone is about as large as a pigeon's egg. It was passed four years ago, and there have been no symptoms since. In rare cases death may result by heart feebleness, collapse or shock, or reflex convulsions during an attack of colic. The number and frequency of the attacks are very variable. It is very rare that a patient has but one attack, for the passage of one stone renders the others movable, and thus we may have groups of attacks that may be repeated at longer or shorter intervals, and may also

remain away for several years. In the majority of the cases the progress of a regular attack of colic is a favorable one; but at any time this regular form may pass into the *irregular*.

The irregular manners of progression may be classified under four headings:—

1. Permanent arrest of the flow of bile.
2. Infectious inflammations of the biliary passages (cholangitis, cholecystitis, abscess of the liver).
3. Ulcerations of the biliary passages, perforation, pericholecystitis.
4. Impermeability of obstruction of the gastro-intestinal canal.

It is evident from a survey of these headings that the irregular courses of cholelithiasis represent or lead to surgical conditions almost exclusively, and accordingly the reader is referred to another part of this work where they are considered from the standpoint of the surgeon.

1. Permanent obstruction to the flow of bile is caused by incarceration of a stone in the ductus choledochus or hepaticus. It is rare that a compression of the common gall-duct is caused by a stone that is wedged in the cystic duct; but strictures and neoplasms that have been caused by gall-stones may also produce the obstruction.

The consequence is a chronic icterus, lasting a very long time, but which is recovered from generally by the passage of a stone through a fistula between the common gall-duct and the duodenum; but sometimes a grave icterus may lead to death. In uncomplicated incarcerations of stone this fatal result is fortunately rare. The evil consequences of a so-called fatal chronic icterus caused by gall-stones are more often due to a carcinoma of the biliary passages. I feel it my duty to emphasize the alarming frequency with which protracted cholelithiasis, that is not operated upon, later on becomes complicated by carcinoma. This is one of the principal reasons why prolonged purely medical, or clinical, treatment by non-operative methods is positively unjustifiable, yes, even criminal.

The conditions mentioned under sections 2 and 3 are described in the surgical portion of this work. I must add that perforation may occur from the gall-bladder outward through the abdominal wall and lead to spontaneous cures. More frequent than this form of perforation are the fistulæ between the bile passages and the intestinal canal. Those between the common gall-duct and the duodenum are the most important. They occur in the neighborhood of the papilla of Vater and resemble the passage of a stone as if it had occurred *per vias naturales*. Perforations into the colon may occur, but those into the stomach and small intestines, into the retroperitoneal tissues, into the portal vein, into the pleura, lungs or urinary passages, and into the vagina are very rare. Perforations into the peritoneum are most dangerous.

Impermeability of the gastro-intestinal canal. It has been observed that dilatation of the stomach was caused by compression of the pylorus by a gall-bladder filled with stones, but this is fortunately rare. More frequent is the obturation ileus caused by obstruction of the intestinal lumen through large stones that have gotten into the intestine through a fistula.

The diagnosis of cholelithiasis is not difficult in typical attacks of colic. It is important to accurately map out the exact localization of the pain. Confusion with intestinal colic, lead, renal and gastric colic, as well as cardialgia may readily occur. Icterus is important for the diagnosis, but, as I have said, it is absent in 55 per cent. of my cases. When very slight attacks of icterus are associated with frequently repeated and painful swelling of the liver, this is very important for the diagnosis. The safest conclusion can, of course, be derived from a demonstration of the stones in the passages. The X-rays or Roentgen rays are of no utility in the demonstration of gall-stone. I have personally placed eight large gall-stones in a row one behind the other and obtained no impression on the plate by Roentgen photography. But the X-rays may be useful when it becomes necessary to differentiate gastric ulcer or gastric carcinoma from gall-stone disease; for, according to my method described in the *Archiv f. Verdauungs Krankheiten*, Berlin, 1906. Ulcers and cancers of the stomach can be made visible and demonstrated by this form of photography.

For the diagnosis of the irregular forms, the previous history of former attacks is of great importance. For all this, see Surgical Section.

For those cases of gall-stone disease which run a regular course, the prognosis is in general favorable; but for those cases which run an irregular course, the prognosis is favorable or unfavorable according to the seriousness of the complications.

*Treatment—Prophylaxis:*—The patient must avoid all foods which might possibly lead to indigestion, and thereby predisposing to infection of the biliary passages. It is very essential to insist on small meals, because a food which in itself is not harmful may bring on an attack of colic by its bulk. A diet that is rich in fats must be strictly avoided. A diet that gives rise to much gas must be strictly avoided; for instance, pease, beans, lentils, sauerkraut, pies, mayonnaises, salads and raw fruit. It is essential to avoid alcohol in anything exceeding one-half a pint of light Rhine wine per day. It is important that the patient should attend to regular evacuation of the bowels, but the strong purgative mineral waters like Hunyadi Janos and Rubinat Condal must be strictly avoided. These powerful mineral purgative waters do more harm than good. Gall-stone sufferers must avoid all clothing that tends to constrict the abdomen.

*Treatment During an Attack of Colic.*—The patient must be put to bed immediately; a hot water bag is to be applied over the liver, and one-fourth grain of morphine is to be injected hypodermically at once. The drinking of small quantities of hot water during the attack, or hot Carlsbad-Sprudel water is to be recommended. When the patient has recovered from his immediate colic attack I recommend to him to continue the use of the hot Carlsbad-Sprudel water morning and evening, one tumbler before breakfast as hot as can be taken; then allow one hour to elapse before taking any food. If a slight chronic icterus continues after an attack of colic, and especially if the liver and gall-bladder regions are sensitive, I advise all patients to continue this Carlsbad treatment for a month. In this period the patient



must lie down for three hours twice daily, say from nine to twelve in the morning, and from three to six in the afternoon, and hot cataplasms must be applied to the liver region during this time. During the first hours in the morning he should drink one hundred cubic centimeters of Carlsbad-Sprudel water every fifteen minutes, as hot as can be taken. In this way the patient may drink six to eight hundred cubic centimeters in a day. If the patient cannot tolerate so much, the amount of Carlsbad water taken can be restricted, particularly in the afternoon. During this treatment, the meals are taken at half past seven, one P.M. and seven P.M.

*Medicinal Treatment.*—Gall-stones cannot be dissolved by any medicines that can be taken by the mouth. All medicines that have hitherto been supposed to have had this power bring about their only apparent and very transient improvement by their anodyne effect. Thus the Durand drops which are composed of one part of turpentine, four parts of ether, twenty to thirty grams of cognac and the yolks of two eggs, act simply as an anodyne. The dose is fifteen to sixty drops. Olive oil, oleate of soda, glycerine, preparations made from bile and bile salts are of doubtful value. But I have seen cases in which the salicylate of soda seems to act as a very effective anodyne, and even reduce the jaundice and size of the liver. We do not know in what way salicylate of soda influences the metabolism of the liver cells, but we do know that it is an intestinal disinfectant to a certain extent, and I have convinced myself that the bactericidal effect of the bile is increased after two days' taking of sixty grains of salicylate of soda in divided doses. These tests were made with the colon and typhoid bacilli. But all this medical treatment should not be continued too long. The dangers from the complications mentioned are too great; especially should the practitioner be cautioned concerning the alarming increase of cancer of the biliary apparatus that is traceable to the effect of gall-stones.

I do not find that gall-stones and acute gastritis, as they present themselves in practice, offer any difficulty in the way of differential diagnosis. The trouble is to diagnose gall-stones from gastric ulcer and membranous colitis. As to the pain of gall-stones, there is too much of the hypothetical about all the speculations on this point. The peritoneum, when inflamed or distended, is always painful. In making a diagnosis from the stools I dilute the feces and sift them through a Boas or Dudley D. Roberts stool sieve.

Certain cases of gall-stones, although they undoubtedly need operation, are in too exhausted a state to stand it. The metabolic cases where the operation shows no infection of the gall-bladder, require careful dieting, Carlsbad-Sprudel, or Bedford Magnesia water. A case which may have originally been due to disturbed hepatic metabolism may later show infection of the gall-bladder.

I do not use cholagogues. There are no cholagogues except those that do harm; even the bile salts, when so administered, injure the stomach. By the time the cholelithiasis is established it is impossible to prevent catarrhal duodenitis, because this as a rule precedes the catarrh of the biliary appa-



tus. In treating this condition, I study the fæces and ascertain what foods are not digested, and exclude them, enjoin rest in bed, hot applications to the abdomen, and order a half-pint of hot Carlsbad-Sprudel water at seven A.M. before breakfast and at five P.M. It is, in my opinion, impossible to dissolve the calculi, and any treatment directed toward this end is bad procrastination.

As soon as a diagnosis of gall-stones is made definitely, and the condition of the patient permits it, I recommend surgical treatment, even if the gall-stones are not due to infection but to abnormal liver metabolism; they must be removed. I have nothing to say about the surgical procedure; my surgical friends attend to that part of it. As regards the direct indications for operation all signs are misleading in these cases, but (1) fever, (2) constant and extreme tenderness over the liver, and (3) leucocytosis are the most reliable signs of suppuration. The mortality in those cases which I was obliged to treat medically is much greater than those which I submit to the surgeon, as cancer often supervenes in cases treated medically.

To diet these patients guardedly, examining the fæces carefully, is the first rule. But there are no hard and fast, cast iron dietetic regimes. The rule to follow is to study and find out what agrees the best. After the operation the Carlsbad waters are very effective in preventing recurrence. A recurrence of the stones, gastritis, enteritis and colitis are the commonest complications. The best prophylactic for those who are inclined to gall-stones is Carlsbad-Sprudel or Bedford water, as hot as it can be drunk, and living on such a diet as has proven itself to be best digested according to the methods above referred to.

[Reprinted from THE HOSPITAL BULLETIN, January 15, 1910]

RELIGION AND SCHOLARSHIP; OR,  
DIVINE KNOWLEDGE AND HUMAN  
KNOWLEDGE.

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Delivered by invitation of the Young Men's  
Christian Association of the University at  
Westminster Presbyterian Church,  
Baltimore, Sunday, Novem-  
ber 21, 1909.

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INTRODUCTION.

When a man of learning becomes a disbeliever there is exultation among the skeptics and atheists. "Behold the fruits of the highest intellectual culture!" they cry. "Behold, the result is the turning away of man from God!" And then follows the enumeration of all men of great intellect who have been agnostics or atheists. Notably around Charles Darwin does the polemic of disbelievers wage most fiercely, for in the "Life and Letters of Charles Darwin" by his son, Francis D., we gain an insight into the process of getting lost in disbelief of the eminent naturalist. On p. 278 of Vol. I of this work we learn that there were chiefly two reasons for this skepticism—(1) the incredibility of the miracles by which he assumes Christianity is supported, and (2) that the old argument from design in nature as given by

Paley which "formerly seemed to him conclusive" failed now that the "*law of natural selection*" had been discovered. Opposed to the first of these reasons are the words of the founder of Christianity Himself, that He did not intend that His religion should be founded on miracles (John iv, 48; Matthew xii, 38 and 39). It is, therefore, a fundamental error when this great thinker assumes (in his "Autobiography," written in 1876) that Christianity needs the support of miracles. Darwin, as the father of the law of natural selection, was led to think more and more objectively, and confesses that as he lost interest in music and poetry, so he forgot how to think spiritually. The father of a new direction of human thinking naturally becomes disinclined to agree with any doctrine that is seemingly at variance with the new law he has discovered. This feeling of antagonism to anything that tended to oppose his mental offering was to be expected. *It will always be strange that it should be thought the safest course to separate as sharply and as widely as we can between that which we are called upon to believe in religion and that which we are able to trace or understand in nature.*

One of the profoundest arguments in the entire range of Christian philosophy is presented by Butler in his "Christian Analogy" concerning this apparent antithesis between religious faith and faith in science. All the steps of the argument of Butler are founded on the opposite belief, namely, that all the truths, and not less all the difficulties, of religion *have their type and likeness in the constitution and course of nature*. This reasoning is as profound as it is simple, and as we follow it

our eyes are ever and anon opened to some new interpretation of familiar facts, and we gradually learn to recognize among the curious things of the earth one after another of the laws which, when told us of the spiritual world, seem so perplexing and so hard to understand.

Concerning the argument that the discovery of the law of natural selection had invalidated the belief in purpose and design, in the results and methods of creation, this has been completely answered by the Duke of Argyle in his "Reign of Law" (see this book and Note A to p. 46) ; also his discussion with Mr. Wallace in the *Journal of Science*. No. 16, October, 1867. After reading these able discourses I believe every evenly balanced mind will feel satisfied that between the scientific conception of the law of natural selection and the religious conception of purpose or design in creation there is no conflict.

Mr. Wallace virtually admits that it dwindles down to this: "It is simply a question of how the Creator has worked." But if we desired any further harmonizing of these apparent discrepancies between fundamental scientific and fundamental religious opinions we find them in Henry Drummond's work on "Natural Law in the Spiritual World."

In this connection I feel it my duty to call attention to the modern tendency of some of the most prominent representatives of natural science to become dogmatic. Dogmatism, which by Haeckel, Huxley and others was asserted to be the exclusive possession of religious people, is frequently observed in scientific arguments, whilst it is claimed with equal firmness that open-minded



intellectual integrity and courage are the characteristics of those that reject Christianity. According to Lyman Abbott, a man of great intellectual distinction who counted himself an agnostic said not long ago of an equally distinguished man who was an ardent Christian: "I don't see how it is possible for so able a man to believe the fairy tale of Christianity. He cannot be entirely sincere." This assumption that a person of superior intelligence must be a skeptic overshadows the faith of many good people. The remark quoted is very similar to those I have personally heard during conventions of scientific men in this country and abroad, where it occasionally becomes evident that among those who lay great claim to liberalism there are a surprising number who are conspicuous for narrowness and dogmatism.

The assumption of the intellectual superiority of the skeptic over the adherent to faith is born of pure arrogance. It has no authority to challenge belief as if it were the sole custodian of truth. In the following sermon on the interview of Christ with Nicodemus I shall endeavor to make clear the particular susceptibility of learned men to lean too much toward objective evidence and to lose the spiritual side of their natures, and even to suggest that faith rests solidly on the largest and most courageous use of reason, by which I mean the full play of all the human faculties, the complete exercise of human knowledge.

In one of the most masterly and scholarly contributions to this subject Josiah Royce says (*Harvard Theologic Review*, October 1909, p. 434, "What Is Vital in Christianity?"): "The world of our usual human experience is but a beggarly

fragment of the truth, and if we take too seriously the bits of wisdom that it enables us to collect by observation of special facts and of natural laws it becomes a sort of curtain to hide from us the genuine realm of spiritual realities in the midst of which we all the while live."

The effort to found a new religion on the basis of *natural law* as revealed and understood by human intellect has been made many times and long before the scholarly attempt by Dr. Charles Eliot, the erudite ex-president of Harvard University (*Harvard Theologic Review*, October, 1909, p. 389). But laws (see Duke of Argyle on the "Reign of Law") do not explain anything except the order of subordinate phenomena in nature. They set forth that order as due to force; they do nothing more. They do not explain the force of which they are the resultant.

Least of all do laws explain themselves. They suggest a thousand questions much more curious than the questions they solve, or, rather, attempt to solve. The very beauty and simplicity of some laws is their deepest mystery. What can their source be? How is their uniformity maintained? All that we ever know is some numerical rule or measure according to which some *unknown forces* operate. But whence come those measures we are not told. They are the result of human speculations, of the operation of our senses. But, unlike the ordinary consciousness, the religious consciousness is concerned with that which lies beyond the sphere of sense.

The unreliability of a religion that is based on what human beings recognize as "natural law" is evidenced by the errors our sense faculties have

been shown to exhibit. The views of today—say of the constitution of matter and the laws of Kepler and Newton that hold matter together—may appear satisfactory to us for the present, but how will these laws be regarded by the physicist at the end of the twentieth century? According to Faraday and Sir William Crookes, we are incessantly learning the lesson that our researches have only a provisional value.

The view of Crookes ("President's Address to British Chemical Society," March, 1880) that all of our chemical elements have been formed from one primordial substance is gaining ground among physicists, and with it the view that all matter now existing is disintegrating at almost immeasurably slow rate and reverting to the state of this single primordial element, which he terms *protyle*. The rate of this disintegration is expressed by Becquerel in his calculation, in which he believes to have shown that one square centimeter of radioactive surface would radiate into space one gram of matter in one billion years, or, according to Crookes, if one million atoms fly off every second it would require a century to diminish one milligram. This fatal quality of atomic dissociation appears to be universal, not only in radium, where it is most active, but in all matter. It operates whenever a piece of glass is rubbed with silk in the ordinary friction machine, it works in the sunshine and rain drops, and in the lightning and flame, it prevails in the waterfall and stormy sea, and although the whole range of human experience is all too short to afford a parallax whereby the date of the extinction of matter can be calculated, *protyle*—the formless

mist, the primordial mother substance of all matter—once again may reign supreme, and the hour hand of eternity will have completed one revolution.

“If thou wouldst know the mystic song  
 Chaunted when the sphere was young,  
 Aloft, abroad, the pean swells—  
 O wise man, hearest thou half it tells?  
 To the open ear it sings  
 The early genesis of things;  
 Of tendency through endless ages  
 Of star dust and star pilgrimages,  
 Of rounded worlds, or space and time,  
 Of the old flood’s subsiding slime,  
 Of chemic matter, force and form,  
 Of poles and powers, cold, wet and warm;  
 The rushing metamorphosis  
 Dissolving all that fixture is,  
 Melts things that be to things that seem,  
 And solid nature to a dream.”

—Emerson.

These are examples of the imaginings of some of the foremost physicists, and upon such speculations it is suggested a religion could be founded—as possibly it could. But if natural laws as we formulate them are based either on speculation or research, and if both of these have only a provisional value, the question is justifiable, What enduring power can a religion have that is built upon such human endeavors? Harnack (“What Is Christianity?”) states a truth of enormous penetration when he declares that it was one of the enduring qualities of religion of Christ that no effort was made to found it upon science—in the



first place, because the domains of religion and science are entirely different, and, secondly, because a religion that would have to change its foundation as often as science has already done could not inspire the confidence of a Divine revelation.

In elaborating on the following quotation from the third chapter of John, I lay no claim to originality in the manner in which the subject is treated. I can only say that having heard it treated in that way by Consistorialrath E. Ohly of Wiesbaden and Dr. Frederick Lynch of New York, I am quoting largely as I remember their sermons:

"There was a man of the Pharisees, named Nicodemus, a ruler of the Jews. The same came to Jesus by night, and said unto Him: 'Rabbi, we know that Thou art a teacher come from God: for no man can do these miracles that Thou doest except God be with him.' Jesus answered and said unto him: 'Verily, verily, I say unto thee, except a man be born again he cannot see the kingdom of God.' Nicodemus saith unto Him: 'How can a man be born when he is old? Can he enter the second time into his mother's womb and be born?' Jesus answered: 'Verily, verily, I say unto thee, except a man be born of water and of the spirit he cannot enter into the kingdom of God. That which is born of the flesh is flesh, and that which is born of the spirit is spirit. Marvel not that I said unto thee, ye must be born again. The wind bloweth where it listeth, and thou hearest the sound thereof, but canst not tell whence it cometh and whither it goeth; so is everyone that is born of the spirit.' Nicodemus answered and

said unto Him: 'How can these things be?' Jesus answered and said unto him: 'Art thou a master of Israel and knowest not these things? Verily, verily, I say unto thee, we speak that we do know, and testify that we have seen; and ye perceive not our witness. If I have told you earthly things, and ye believe not, how shall ye believe if I tell you of heavenly things?'—*John iii, 1-12.*

FIRST EARTHLY THINGS, THEN HEAVENLY.

It is much to be regretted that more of the conversation of Jesus with scholars of His day and with strangers have not been recorded, for in these familiar talks He said some of His greatest and most far-reaching things. Here in this formal conversation with Nicodemus He uttered the foundation truth of religion, namely, the Divine spirit of God reaching down and lifting men up into the kingdom of heaven. That is the beginning and end of religion. This conversation is especially interesting because it is with a scholar, and Jesus had very little contact with the educated men of Israel. Nicodemus was a learned lawyer and was very much interested in religious questions, particularly their intellectual and political aspects. He had, doubtless, as the chief desire of his life, the restoration of the kingdom of Israel. Stirred by his prophetic books, he was eagerly watching for signs of its approach. John the Baptist's preaching, that it was near, may have awakened in him renewed expectancy. Anyhow, he eagerly follows Jesus and becomes intensely excited over His deeds and words. As soon as night comes, when he can find Jesus alone, he seeks Him, and then ensues one of the

most interesting conversations ever held. Of course, we have only a fragment of their talk. Perhaps they talked long into the night. But we have enough of outline to reconstruct it.

Nicodemus says to Jesus that he has heard Him preach, and, although much interested, could not understand His teaching; but he was very much impressed by His miracles, and knows that He must have come from God and that God is with Him, otherwise He could not do those wonderful things. Then Nicodemus must have told Jesus that He was just the man to take hold of the Jewish people and gather Israel about Him and establish the kingdom, set the church on its old foundations and bring back the departed glory of Zion.

Then Jesus must have spent a long time in disabusing Nicodemus' mind of this false idea of the kingdom, showing him its real nature—how it was an inward kingdom, independent of States or churches, strength or weakness, riches or poverty; how it was a state of being, a disposition, a communion with God, the eternal life.

Nicodemus listens absorbedly, but at last exclaims: "It is beautiful, wonderful, but I cannot understand, I cannot see it."

Then Jesus utters the one great secret of all spiritual living—"Except a man be born anew, born from above, he cannot see the kingdom of God."

But all this was utterly outside Nicodemus' experience, and he vaguely shakes his head and says: "How can an old man be born again?"

Then Jesus repeats and explains: "Except a man be touched and awakened from above by the

Spirit of God he cannot find the way into the kingdom. That which is born of flesh is flesh, and can comprehend only fleshy things; that which is born of the Spirit is spirit, and can comprehend the things of the spirit. Just as the wind roams over the earth, doing its mysterious work, and man can only wonder and have no power over it, so the Spirit of God touches the hearts of men in the same mysterious way and works its holy wonders in them."

But Nicodemus had neglected his spiritual nature, and this is all foreign language to him. And Jesus is surprised and somewhat impatient, and exclaims: "Art thou a teacher of religion in Israel and know not the simple beginnings of religion? If you have not believed and lived the simple earthly principles of cultivating the spiritual life and common virtues which you have heard Me teach, how can you understand and believe if I tell you heavenly things?" Then Jesus goes on to explain His own relation to the kingdom. And late in the night Nicodemus goes home to ponder these things, and he ponders them to his redemption, as we shall see.

This is about the way in which Consistorialrath Ohly and Frederick Lynch interpreted this fascinating discourse. Now as to our deductions.

"Unlike the ordinary consciousness, the religious consciousness is concerned with that which lies beyond the sphere of sense. A brute thinks only of things which can be touched, seen, heard, tasted, etc., and the like is true of the untaught child, the deaf-mute and the lowest savage. But the developing man has thoughts about existences which he regards as usually intangible, inaudible,



invisible, and yet which he regards as operative upon him."

So says Herbert Spencer. If this be true, then he who is more than a brute, who thinks sometimes of what cannot be touched, seen, heard, tasted, etc., will be interested to know what one of the greatest religious teachers of the ages has to say about the one great Being who is intangible, inaudible, invisible, and yet is operative in mankind. What does Jesus teach about God? And this question will interest the thoughtful man, whether or not he thinks that Jesus possessed a Divine or even an exceptionally prophetic character.

Herbert Spencer has said that nothing is more certain than that we are ever in the presence of an Infinite and Eternal Energy, from which all things proceed. At least twenty-odd centuries before Herbert Spencer an unknown Hebrew poet had said the same thing:

"Whither shall I go from Thy Spirit?  
Or whither shall I flee from Thy presence?  
If I ascend up into heaven, Thou art there;  
If I make my bed in hell, behold, Thou art there;  
If I take the wings of the morning  
And dwell in the uttermost parts of the sea,  
Even there shall Thy hand lead me,  
And Thy right hand shall hold me."

What did Jesus teach concerning this intangible, inaudible, invisible, yet universal Presence?

First of all, that the "knowledge of God is not school knowledge; it is life knowledge; not information, but acquaintance." "God is not to be

known by reasoning out doctrines of Him, but by living with Him." "A man is to know God as a child knows his parents—by experience." So, for the answer to the question, What did Jesus teach? we are not sent merely to the Four Gospels. We are sent to the experience of the pupils of Jesus. What is the conception of God which has grown up in the experience of Christians out of the teaching of Christ? Or, to turn back to the phraseology of Herbert Spencer, if the developing man has thoughts concerning the invisible but universal presence, what are the thoughts of those who consciously owe their religious development to the teachings of Jesus Christ?

Christians universally believe in a personal God. What do we mean by a person? Why am I, I; and you, you? We mean consciousness and choice; some knowledge of ourselves, and some power to direct ourselves, or, in more technical language, self-consciousness and self-determination. In the experiences of all Christians, and in the teaching of Jesus that has come down to us, this is the first and most fundamental truth. This inaudible, invisible, universal Presence, this Infinite and Eternal Energy from which all things proceed, is one who is related to men, one between whom and men communion, fellowship, converse is possible. This Presence is "*Hc*," not "*It*." Says Matthew Arnold: "Many excellent people are crying out every day that all is lost in religion unless we can affirm that God is a person who thinks and loves." These many excellent people are right in so far as this: it is true that what is most fundamental in the Christian religion is lost unless we can affirm that God is a person who thinks

and loves. For the whole of the Christian religion might be said to be summed up in the words, "Say, Our Father." For it all grows out of the faith that Christian experience is common to humanity—that is, religion is a common, and may be a universal, experience, and that it is an experience of conscious filial relation to the Infinite, who is never perfectly understood, but need never be unknown. Christianity does not approach God as a Great First Cause—that is, through philosophy; it approaches Him as the Great Companion—that is, through experience.

One more illustration must suffice here to complete this hint as to a doctrine of God built out of human experience. What do we mean by the transcendence and what by the immanence of God? What is there in personal experience which answers to these phraseologies? Two truths of universal consciousness: I am more than the body which I inhabit, and it is subject to me—a truth which psychology may interpret or explain, but can never successfully controvert. But I am also equally present in all parts of my body, and in a state of health it is all alike a part of my domain. Use this human experience to interpret God's relation to the universe. First, God is Spirit and transcends the universe. "He, and He alone, exists in and of Himself, \* \* \* while the universe, His sole companion in existence, exists simply and solely because of Him. He is the Creator; it is the creature. His is the will, and the universe is the response. In self-existence and creatorhood He stands transcendent." And, second, this transcendent Spirit is no absentee God, detached from the universe, a localized Deity

dwelling in the sky, as still many hymns and prayers represent Him to be. "All opportunity to think of an infinitely distant home of God is crowded out, and it is by a practical necessity that we look upon Him as a pervading Presence. If we are to think of Him as anywhere, we are compelled to think of Him as everywhere." In this respect, as we have already pointed out, the scientific conception, as interpreted by Herbert Spencer, and the spiritual conception, as interpreted by the ancient Psalmist, are essentially one. The testimony of religious experience modern science confirms. (Lyman Abbott.)

There are two great truths of universal import in this conversation. The first is this: The way to enter the kingdom of God is not so much by effort, not by acquiring great knowledge, as by response to the Spirit of God. There are two kingdoms—a kingdom of the flesh and a kingdom of the spirit; a kingdom of the animal and a kingdom of the soul. Every man is born with power to respond to the impact of these two kingdoms. Food, air, water, all kinds of natural powers, beat in upon him from the world and develop his body if he will let them. Likewise, says Jesus, Divine forces beat in as winds upon man's soul to quicken his soul-life if he will let them. Man is meant to keep both sides of his nature open to these double influences from birth and let his life be developed in proper harmony. It was not many years ago when men said that during the first 15 or 20 years of a man's life, during childhood and youth, let him be responsive to the fleshy influences only; then suddenly bring the spiritual influences upon him with tremendous force, and



let them pry open his heart and take it so as by force. This was the false idea that Bushnell fought so hard. It was contrary to nature. His contemporaries accused him of not believing the truth that a man is born into the kingdom from above. Bushnell answered, in substance, that he believed it with his whole heart even more than they did.

"Only," he said, "it ought to be contemporaneous with physical development. You immediately put the child under fleshy influences, and he is gradually adjusted to the natural kingdom; so, also, put him under spiritual influences and let them lift him up into the kingdom of God."

And Bushnell was right. Today we are trying to rear children so that they shall be simultaneously fed from both kingdoms. In the normal life these two processes develop side by side—the body fed from earth, the soul nourished from heaven.

But how many men respond only to the impacts of earth and belong only to the earthly kingdom? How many men pass into old age hardly feeling one quickening, regenerating touch of those breezes that sweep the earth from the spirit world? They are not always nor necessarily bad men, but they have nothing higher born within them than earthly forces can generate. They have felt the impact of the earth and air, of work and comradeship, and have sometimes risen high from earthly impellings. Nicodemus was just this type of man. He had been born, as is every man, with power to respond to the two kingdoms—the seen and the unseen, the human and the Divine. Jesus saw at a glance that he had lived

entirely in the seen world and been shaped by its forces only. His idea of the kingdom was material. He was interested in miracles and theology—all the concrete, earthly sides of religion. His ideals never rose beyond prudence; his aspirations never soared above the earth or beat against the sky; his nature had not throbbed and bounded to anything intenser than the thrills of earth. Now, to Nicodemus, and to us all, Jesus says that just as a man is adjusted to the natural world and born into the power of the fleshy kingdom, not alone by efforts of his own, but by submitting himself to the impact of the world forces, so a man is born into the kingdom of God by humbly opening his heart to the incoming of the Divine Spirit and letting it shape him into harmony with the things of heaven.

There is a Divine, heavenly, spirit force in this world. It is just as real as earthly forces. It is more real, for it rules them and is above them. It is the Spirit of God Himself. It is God—operative, energizing, redeeming men. It is the soul of the universe, everywhere present. It is here, beating against the human heart, as the ground beats against the feet or the winds against one's cheek. To get into this kingdom one who has lived only in the fleshy kingdom must open wide the windows of his heart, make the heart clean, pure and inviting, pray, live a life conducive to the Spirit's entrance, cherish the Spirit when it comes, make the chief end of life to keep responsive to its touches, and thus let himself be born, regenerated, quickened from above. With the Spirit's entrance new, heavenly powers will pulsate through our frames. Our souls will swell with refreshing

currents. New visions will flash upon us far surpassing earthly landscapes. New truths will fall into the mind far beyond man's finding. Ideals will spring up that burn like stars. Purposes will grow to find their consummation in other worlds. For, with the Spirit comes the consciousness of immortality. The kingdom of God is an eternal kingdom. To be born of it is to become one with its eternity. Peace will come, for peace is the gift of God. Life will bring forth new virtues, new beauties, new heroisms, new powers to love and suffer. We will live by new laws and diviner motives, lean on new arms, live with new friends, have our life in God. "Like an exotic plant in a temperate zone, the soul without God bears only leaves." With God it bears heavenly fruits and takes His likeness upon itself.

This, then, is the way into the kingdom. Unaided, man may go far, but for entrance into the full-orbed glory we must be born into it by the touch of the Divine Spirit from above.

To be born from above—how we all need it!—need to be made over even every day, need psychic cleansing, regenerating, lifting into higher life! How we need to be born again in our purposes! How we need to have our loves exalted and purified, our emotions deepened and sanctified, our interests expanded, our hearts cleansed, our sins washed away by the Spirit's cleansing presence! How we need enlargement of life, our lives transformed and transfigured by the glory of God's abiding presence! How can we be long content to live in the small kingdom of the earth when the other kingdom, with its glories, lies just above and around us and stoops down to lift us

up when we yield? We belong to the kingdom of God by nature. We have strayed from it, kept ourselves from its blessed fields. But it is ours if we will. Said Jesus, "Come ye blessed of My Father, inherit the kingdom prepared for you from the foundation of the world."

Let us now look at the other and closely allied truth which Jesus emphasized in this conversation. It has to do with the comprehension of religious truth. He gives here a helpful and universally true motto, a natural and unfailing way of approach to truth: "First earthly things, then heavenly." Nicodemus had been seriously trying to comprehend the new doctrines Jesus taught. He was a good man and really wanted to understand these doctrines, but they were too transcendent for him. We today cannot realize how transcendent Jesus' teachings were to an Israelite. Jesus sees Nicodemus' trouble, and says: "Nicodemus, you cannot understand these heavenly things until you have fulfilled their earthly requirements." That is, according to Jesus, it is not by cold, abstract processes of reasoning that Nicodemus could get insight into the higher spiritual laws, but by a process of living. He could not understand heavenly things until he was filled with an enthusiasm for Godlike life here on earth.

It is a great truth. Earthly virtues are the paths over into heavenly truths. The virtues come first. We walk over into the meaning of the doctrines of the kingdom by obeying its laws. "He that doeth the will of God shall learn of the doctrines." If we want to understand the lofty things Jesus taught, we must walk with Him in lowly ways of love and duty. Forget your mental



troubles and live in His Spirit, and the truths He taught will grow luminous. Sometimes the way to seek spiritual truth is not to make any special efforts to seek it, but by holy living prepare yourself to let it break in upon you of its own will. It will come when the heart is ready. None of the disciples understood Jesus' teaching during the first few months they followed Him. Instead of explaining His doctrines, He said: "You will hear when you have ears to hear," and set them to living His commandments. After a while the deep meaning and mystery of the truth came—silently, unsought, as the dawn comes. Children first learn to speak the language; by and by, with the years, the meaning comes. If we live the Sermon on the Mount, by and by we can understand the last chapters of John—first the natural, then the spiritual; first doing, then knowing; first life, then its meaning; first earth, then heaven.

Or we can put this same truth another way—spiritual vision depends on spiritual manhood. Moral enthusiasms must precede heavenly mysteries. There is a beautiful verse in the Revelation which, in speaking of the heavenly music the poet heard in his vision, says, "But no man could learn that song excepting them which had been redeemed from the earth," which is only another way of saying that only the pure in heart can hear heavenly voices or see God. If we wish to see heavenly things, we must cultivate the eye of the soul—make it single, pure. Spiritual truths are revealed to the spiritual man. God is spirit, and they who would know Him must know Him in spirit and in truth.

Who knows but that if we today would make

our hearts as pure as were the hearts of prophets and disciples of old we might have such visions again of God in His world? I myself have an unfaltering conviction that if God's voice is not heard today as distinctly and gloriously as it was heard by the writers of the Bible, it is not because God is not trying to say just as great and as important things to us, but because we are not religiously sensitive enough to hear. I see no reason why Bibles should not be written today if men would only make themselves as spiritually sensitive to God's presence as men were in the older days. God is not absent, neither does He speak to one time and neglect another. If we see Him not today, it is not because He is not here, but because our vision is clouded. May it not be that when we have passed through this period of materialism in which now we rush and strive, and turn again to the things of the soul and reach out for the higher life, new prophets shall arise and new books of God be written, and new psalms be sung, and there be open vision again of God's presence here on earth?

Or, to put it in still another way, one must enter into the spirit of a thing before he can understand it. The reason Nicodemus could not comprehend what Jesus said about the kingdom was because he was not in sympathy with it spiritually. So Jesus says to him: "It is vain for Me to try and explain the Divine mysteries of My kingdom, Nicodemus, while you have no sympathy with the kingdom itself." This is the heart of the matter. We cannot comprehend the beauties of Divine things until we enter into oneness with their purpose. We see the meaning of things according to

the spirit that animates our searching. The artist looks at the landscape and sees a thousand beauties hid to common eyes. To enjoy music to its fullest extent we have to know its laws and make for ourselves poetic natures. In all things we have to bring ourselves up to the level of that which we should comprehend. The universe is full of the revealings of God. No man would dare hint at the thousands of even natural forces as yet unfelt and unseen—unfelt because we have not yet developed ourselves enough to feel. When we develop our mental sensitiveness up to a certain point a new world of stars bursts in upon it or a Roentgen ray. One of the zests of living is the consciousness that as we grow in mental receptiveness new and wonderful things out of the unseen world will flood our minds. So, too, as we learn to love spiritual things and become possessed with a great enthusiasm for the kingdom of God, and go out into life looking and longing for God, and make our souls sensitive to Divine and holy things, there shall grow up within us an abiding sense of the nearness of the blessed Spirit presence, and secret mysteries of heaven shall begin to unroll their meaning before our eyes, and streams of power and plenty begin to roll in upon us out of unseen worlds, and all the earth begin to glow with the glorious presence of the Lord. First the trained and sympathetic heart, then the kingdom; "first earthly things, then heavenly."

We are fortunate enough to know that Nicodemus followed these rules we have been studying and that they brought him into the kingdom. For, two years later, when the Jews would sentence Jesus without trial, we find Nicodemus pleading

His cause, and, at the last, we find him, in his great devotion, doing honor to the dead body of the Lord; for, says John:

"There came also Nicodemus (which at the first came to Jesus by night), and brought a mixture of myrrh and aloes, about a hundred-pound weight. Then took they the body of Jesus and wound it in linen clothes with the spices, as the manner of the Jews is when they bury."

This was the truest indication that Nicodemus then understood the teachings of Christ, because his was a great sacrifice to give up his lordly station in the Jewish hierarchy of that day and become a disciple of the Lord.

"Wherever through the ages rise  
The altars of self-sacrifice,  
Where love its arms has opened wide  
Or man for man has calmly died,  
I see the same white wings outspread  
That hovered o'er the Master's head."





# The Pathologic Physiology of Digestion and the Modern Methods of Diagnosis and Treatment Based Thereon

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*Reprinted from*

THE DIETETIC AND HYGIENIC GAZETTE

April, 1910



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## I. PHYSIOLOGY AND PATHOLOGY OF GASTRIC DIGESTION.

MANY of the older authors, beginning with the American physiologist, Wm. Beaumont, believe that the mechanical irritation of the foods cause the gastric secretion, but the experiments in Pawlow's laboratory, in the institute for experimental medicine, St. Petersburg, have proved the fallacy of this view. In the first place, if the secretion were due to simple mechanical irritation, there is no reason why irritation with the point of a glass rod, with a feather, or with sand placed in an animal's stomach, should not cause the secretion also. The mistake of the older experimenters, according to Pawlow, grew out of the fact that they ignored the so-called psychic secretion—a secretion which can be set up by the mere sight or smell of food, or even a very intense feeling of hunger. If the esophagus of a dog is cut, and its end sutured to the edges of the abdominal wound, or allowed to open above the serum in the neck, and at the same time a gastric fistula is established, pieces of meat which are fed to the dog after recovery from these operations will not reach the stomach, but fall out of the upper end of the fistula leading into the esophagus. Nevertheless, in five or six minutes after swallowing the food, which never reaches the stomach, gastric juice begins to be secreted, running from the gastric canula first in drops and afterwards in a continuous stream. If the dog be of-

fered meat without receiving it, the gastric secretion will also appear, though not so plentifully as when the dog was actually allowed to eat the meat. A further interesting phenomena observed in these dogs was that no secretion followed the swallowing of indigestible substances like small stones. These experiments furthermore elicited the astounding fact that for every kind of food a definite gastric secretion is formed of specific composition. Therefore we can say that the stomach provides a certain chemical composition of gastric juice to meet each case. We must therefore conclude that the mucous membrane of the stomach is capable of distinguishing between the varieties and classes of food that come in contact with it, much as the skin recognizes mechanical, chemical, thermic and electrical stimulation. The question might be asked, "What is the object of this psychic secretion?" for Pawlow has clearly established the existence of two kinds of gastric secretion, the chemic and the psychic. This question applied to the human physiology would be the same as inquiring, "What is the object of appetite?" The answer is that under the influence of the psychic secretion a gastric juice is furnished which is much more effective than that which is secreted under purely chemical stimulations of the food, *i.e.*, when food is taken without any special appetite. Furthermore under the influence of psychic secretion, foods which otherwise would not stimulate the gastric mucosa to secretion become converted by



the already present psychic secretion into something else which constitutes a further stimulant to the secretion of gastric juice. For instance, if a solution of albumin be introduced into the stomach of a dog, upon which a Pawlow operation has been performed, *i.e.*, splitting off part of the stomach with all the vessels and nerves intact, and making this second smaller stomach communicate with the external abdominal wall, but not with the general cavity of the large stomach from which it is dissected (see *International Clinics*, XII, p. 276), there will be no secretion. But if the psychic secretion is set up by some other means, before the albumin is placed in the large stomach—for instance, by waving a piece of meat before the dog's eyes—then following the introduction of albumin, a secretion will be found in the small stomach which is qualitatively greater than the psychic secretion alone, or when albumin is given alone; it is evident that while albumin in itself does not excite secretion, the products of albumin do cause this secretion. The same is true of pieces of bread which when placed in the large stomach through the fistula will not promote secretion, but if the dog is allowed to swallow the bread, secretion commences and continues for several hours. Psychic secretion therefore, is a preparatory secretion transforming substances which would otherwise not stimulate the stomach, into such conditions which can accomplish the stimulation. The fact that bread will cause a secretion when chewed and swallowed and not when placed directly in the stomach through the fistula, may be interpreted (as Pawlow and Peter Borisoff do), as proving the secretion of a gastric juice under psychic influence, but—as I will show presently—it may be due to a special internal secretion of the salivary glands that stimulates gastric secretion.

*An Internal Secretion of the Saliva, the Secretion of the Gastric Juice.*—One of the first truths which the seeker for information must try to understand is this: the various juices which bring about the transformation

of the food are not secreted under a simple mechanical stimulation, but they are controlled by a beautiful chemic and nervous mechanism. These are spoken of as the nervous control of gastric secretion and the chemical co-ordination. Concerning the psychic secretion of gastric juice we are already familiar. In this no food whatever enters the stomach; an impression is made on the mind through the sense of smell or sight, which is transmitted to the secretory cells of the stomach through the vagus nerve. During normal digestion this probably occurs to a certain extent, but this secretion does not account for the whole of the gastric juice that is secreted as a result of a meal. For, if both vagus nerves are divided in an animal, it is found that the introduction of meat into the stomach is followed after a period of twenty to forty minutes by a secretion of gastric juice. Now this cannot possibly be a psychic secretion, nor can it be under nervous control at all, for the division of the vagus nerves severs the direct connection of the stomach with the brain. Gastric juice secreted in response to a normal meal really consists of two parts. First, a large amount of secretion which begins within five minutes of the taking of food and is determined and controlled by a reflex nervous mechanism described above. Second, a subsequent portion which is excited by the presence of food in the stomach. Edkins has shown that during digestion a chemical substance is formed within the mucosa of the pyloric end of the stomach, which is absorbed into the blood and then stimulates the secretory cells of the rest of the stomach to active secretion. In this instance the chemical substance which stimulates the peptic glands to former secretion is developed in the mucosa itself, of the pyloric end of the stomach. There are other chemical substances which can stimulate gastric secretion which need not be formed in the mucosa of the pyloric end of the stomach, the antrum, but which are already contained in the food. The substance which Edkins first discovered he called "*Gastrine*," the sub-

stances which are contained in the food which stimulate gastric secretion, were called by Schiff "*Peptogenes*," but the best name to adopt for such substances is that first suggested by E. H. Starling, of London, namely, the term "*Hormones*," from the Greek word meaning to arouse, to excite or to stimulate. All chemical substances that stimulates any kind of secretion under physiologic conditions can be classed as hormones. We have learnt to know now three mechanisms that control gastric secretion: 1st, the psychic of purely nervous secretion; 2d, the secretion by hormones in the pyloric end of the stomach; 3d, secretion obtained by hormones in the food, but there is also a fourth mechanism of secretion which reveals an intensely interesting chemical co-ordination between the secretion of the salivary glands and the secretion of the stomach.

*Probable Stimulating Effect of Salivary Extracts on the Secretion of the Stomach. —Probability of an Internal Secretion of the Salivary Glands.* Up to the year of 1907 it was believed that the salivary glands produced only one secretion, namely, the saliva, which is poured into the mouth to facilitate swallowing and which contains a ferment ptyalin and which converts starches into sugar, but in that year J. C. Hemmeter published his experimental and clinical investigations proving that the salivary glands probably form also an internal secretion during their active stage, which is not poured out into the mouth through the salivary ducts, but which passes into the blood and on reaching the stomach causes a secretion of gastric juice. When the salivary glands were removed from dogs the gastric secretion gradually diminished qualitatively and quantitatively and within a week after the excision of the salivary glands occasionally no gastric juice was formed in the stomach of such dogs. As we know from the experiments of Edkins already quoted (*Journal of Physiology*, Vol. 34, 1906) there is a secretory hormone formed within the mucous membrane in the

pyloric end of the stomach, the fact that the gastric secretion greatly diminishes after the removal of the salivary glands indicates that the pyloric hormone of Edkins either depends for its formation upon previous stimulation by the salivary secretin of Hemmeter or it may depend upon previous psychic secretion. In human beings in whom the salivary glands are destroyed by disease a condition known as "*Mickulicz Disease*," Hemmeter discovered that the gastric secretion was either reduced or lost, but that it was resumed again and became normal when Mickulicz Disease was cured; he also prepared an extract from the salivary glands which contained a stimulating substance to gastric secretion. When this substance was injected into the circulation of dogs who had lost their power of forming gastric juice as a consequence of the removal of the salivary glands the injected salivary extract brought about a partial resumption of the secretion of gastric juice. This strongly suggests the partial dependence of gastric secretion upon some internal secretion formed by the salivary glands, is a proof of the admirable correlation and chemical co-ordination between the function of the salivary glands and the function of the stomach. In the article on "*Diseases of the Intestines*" the writer has described a similar correlation between the function of the stomach and the function of the pancreas and upper parts of the intestines and Frouin has shown (*Soc. de Biolog.*, 1904, 1, p. 461 and 1905, 1, p. 702) that it is possible to stimulate the secretion of the intestinal juice in the middle part of the ileum by intravenous injection of intestinal juice gained from the duodenum or by extracts made from mucous membrane of the upper part of the intestine. The teleologic significance of such a chemical mechanism is clear. A certain constituent of the intestinal juice which is formed under the influence of the food is absorbed into the blood circulation (similar to the formation and action of the gastric hormone of Edkins, see above) and then stimulates the secretion of intestinal



juice in a part of the mucous membrane further down in the intestinal canal. Thus any part of the alimentary tract is normally always prepared for the reception and digestion of the food mass, actually before the food gets there; thus to recapitulate the digestion in the mouth meets with already formed saliva; for the smell, sight and taste of food start up a secretion of saliva. The same psychic secretion occurs in the stomach as a primary phase of gastric digestion, but the secondary phase of the secretion of the stomach depends upon the stimulation by two, perhaps three, chemical substances: 1st, the salivary hormone of Hemmeter, secondly, the pyloric hormone or gastrine of Edkins, thirdly, the hormones or peptogenes contained in the food. The pancreatic and duodenal secretions and the mechanism controlling the secretion of bile are described in the article on the "Diseases of the Intestines." There it will be seen that the secretions are already in the duodenum before the food reaches it. The preparation of the intestine further down has already been described in quoting the work of Frouin, thus one part of the alimentary tract, which is between 25 and 28 feet long in the human being, depends upon work and hormones of the preceding portion for the normal performance of its work.

In the following a brief description of the organic and functional diseases of the stomach will be given. The principal organic diseases by that term means those diseases which are associated with a demonstrable change in the anatomic structure of the stomach. These structural alterations are frequently visible to the naked eye, but certainly can be demonstrated by the microscope. The principal forms of these organic diseases are: (1) acute and chronic gastritis; (2) ulcer of the stomach, fissures and erosions; (3) cancer of the stomach; (4) dilatation of the stomach; (5) displacements or gastropexia. The principal functional diseases of the stomach are usually designated as the neuroses. By this term we mean those diseases which are not

associated with and demonstrable in the changes of the stomach. The term neuroses indicates that these diseases are in some way brought about by the action of morbid nerve function. As there are principally three functions of the stomach: (1) sensation; (2) motor function or peristalsis; and (3) secretion. We may have neuroses of these three types, namely, sensory, motor and secretory neuroses. But it must be borne in mind that no hard and fast line can be drawn between the organic and nervous diseases of the stomach. There are organic diseases of the stomach which are regularly associated with the signs and symptoms of a neurosis, in other words, combined organic and neurotic diseases may exist in a patient. Enteroptosis or displacements of the abdominal viscera is always associated with nervous symptoms. In fact, one may say with enteroptosis there is a congenital infirmity of the entire nervous system. The cardinal point to decide in studying a patient with a disease of the stomach is whether it is an organic or functional disease because the entire treatment depends upon this decision. Organic stomach and intestinal diseases are as a rule local and therefore the treatment is largely local, but functional nervous or reflex diseases of the stomach and intestines are merely partial phenomena of other constitutional diseases or diseases of other organs. They cannot be treated locally, therefore, but must be treated on the basis of the fundamental disease of which they are merely a secondary consequence. It often happens in neuroses of the stomach that the local symptoms restricted to the stomach itself, which may not be diseased at all, are so intense as to divert the attention of the examiner away from the fundamental diseases which is really in some other organ. Two-thirds of all chronic diseases of the stomach belong to the type of the neuroses or functional diseases. This alone is sufficient to emphasize how important this class of disease is.

The examination of a stomach patient might be considered under three headings:

(1) recording the history of the patient, especially the previous history or the Anamnesis, with all the subjective symptoms; (2) the physical method of examination by palpation, percussion and inspection; (3) the chemical and microscopical examination.

*Causation*—That diseases of the stomach are on the increase in the United States is certain and the causes are to be sought in the strenuousness of the American. Their incorrigible tendency to overdo things mentally and physically, not enough rest or recreation, defective social influences, poor nutrition, unsanitary dwellings and cares concerning the daily bread among the poor, on the one hand; and enervating excesses in wines and other alcoholic beverages and psychic insults among the well-to-do. The power of these influences introducing diseases of the stomach is very great.

*Acute gastritis, acute catarrh or inflammation of the stomach is caused generally by overloading of the stomach with indigestible articles of diet, or of foods that have undergone decomposition.* In some rare instances it is due to some micro-organism which has gained access to the stomach. The disease has sometimes been called gastric fever. In summer acute gastritis is most frequently caused by overloading the stomach with fruit or salads in combination with the abuse of cold drinks, especially beer.

*Symptoms*.—Indigestion, nausea, vomiting, feebleness, loss of appetite, diarrhea. It often begins with a chill followed by fever. There is an *acute dyspepsia* which occurs without fever or diarrheas, and is caused by errors of diet in anemic and neurasthenic individuals. The only symptoms are pressure in the stomach, fullness and loss of appetite. The *Treatment* consists in evacuating the stomach, either by the stomach tube or by an emetic. Medicines are rarely needed, but diet must be excluded for two days, and when the food is resumed only thin soups or rice or farina in bouillon and very soft-boiled eggs are permissible.

*Chronic Gastritis or Chronic Catarrh of the Stomach. Causation*.—(a) Abuse of alcohol and tobacco; (b) abuse of laxatives and purgatives; (c) imperfect teeth and defective chewing; (d) hasty eating and bolting of the food; (e) improper diet. Chronic gastritis may be primary or secondary. The primary form is brought about by direct action of the harmful agents on the stomach itself. The secondary chronic gastritis occurs as an accompaniment of other diseases of the stomach or of the diseases of other organs. Thus, we may have secondary chronic gastritis in association with cancer of the stomach and with obstruction of the pylorus, and we may have it as a secondary disease consequent upon heart disease and upon diseases of the liver, kidney and other organs. Chronic gastritis cannot be recognized without chemical analysis of test-meals drawn by the stomach tube. This is unavoidable for the treatment, because the chemical analysis may reveal diagonally opposite derangements of secretion. For instance, we may have excess of hydrochloric acid (gastritis hyperacida) or entire absence of hydrochloric acid (gastritis anacida) which would naturally call for widely different treatment. But there are also other important differences between the different forms of chronic gastritis, which can only be found out by chemical analysis of the stomach contents, a procedure which is unavoidable for the correct diagnosis and treatment of this disease. The disease naturally varies also according to the length of time it has existed, for if neglected the chronic gastritis may continue on until the entire structure of the stomach is destroyed.

*Symptoms* (Subjective).—Feebleness, loss of appetite, perverted tastes, oppression, fullness and distention in the stomach, especially after foods that require a sound digestion. After soups and other liquids these symptoms are not present. It usually comes after beef, hard bread, smoked meats, hard-boiled eggs, and pieces of potato have been eaten. Actual pain and vomiting are not frequent symptoms. The *objective*



symptoms that are of importance can only be ascertained by analysis of test-meals. Whenever there is chronic diarrhea it is absolutely necessary to examine the stomach's contents even if the patients have no stomach symptoms. As there are various types of chronic gastritis which must be treated differently, and must even have a different diet, it will not be practical nor expedient to give the *treatment*. For without a knowledge of test-meals or examinations of the stools, which require a good deal of technical training, it is impossible to have a correct diagnosis of the *treatment*. The *treatment* may be (1) dietetic; (2) hygienic; (3) by medicaments; (4) by physical methods; massage and washing the stomach; (5) by baths and the use of mineral waters. The use of all these methods require such trained experience that reference must be had to special works on this subject for complete detail (see Hemmeter, "Diseases of the Stomach." Published by P. Blakiston's Son & Co., Philadelphia, Pa.).

*Ulcer of the Stomach.*—This is a loss of substance of the gastric mucosa, varying from the size of a pin head to that of a silver dollar or even larger. They may penetrate all the layers of the stomach and cause perforation. They occur most frequently on the small curvature or in the pyloric end of the stomach.

*Causes.*—The fundamental cause underlying peptic ulcer of the stomach is a lessened power of resistance of the mucous membrane of the stomach. This lessened resistance is local and dependent upon disturbances of the circulation in the stomach. When the mucosa is injured either by some sharp or pointed substance such as may accidentally be swallowed, for instance, pieces of egg and oyster shell, fish bone, nutshells, hard seeds, then the defective circulation and impaired resistance to the gastric juice bring about a kind of self-digestion of the injured spot, which eventually develops into an ulcer. But there are toxins that originate from the colon in the

digestive tract of the patient himself and which when absorbed for long periods of time may bring about gastric ulcer independent of any local injury.

*Symptoms (Subjective).*—Severe pain called epigastralgia, severe, cutting and burning in character. The pain in the same case, as a rule, always occurs at the same time after food has been taken. When the ulcer is at the pylorus the pain does not occur until two or three hours after eating, and is frequently accompanied by the vomiting of highly acid gastric contents. These pyloric ulcers most often lead to dilatation of the stomach because they produce a stricture or obstruction of the outlet of the stomach, but pyloric ulcers may cause spasmodic constriction and closure of the pyloric or ring-muscle at the outlet of the stomach. When an attack of violent epigastralgia with vomiting of acid liquids occurs between 6 and 7 o'clock in the evening or between 1 and 2 o'clock in the morning (these are the hours at which the stomach evacuates its last portions, if the meals have been taken at regular hours) we generally have to deal with an ulcer at the pylorus. *Objective symptoms:* The most important of these are vomiting of blood, the presence of blood in the stools, and the existence of excess of hydrochloric acid in the contents of the stomach.

*Treatment.*—The diet is the most important consideration in the treatment. Some cases are so severe that for weeks no food at all can be allowed by the stomach, the patient must absolutely rest in bed, and be fed by nutritive enemas. Then, as the symptoms improve the following foods are allowed by the stomach: soups made of farina, egg and bouillon, raw eggs, gelatines, tea or chocolate with cream, boiled and thoroughly strained oatmeal, rice or farina. Later on broiled sweetbread and calves' brain are permissible. The passing over to the meat foods should be very cautious and slow, as there is great excess of acid in the gastric juice, alkalies, must be taken after the food. One of the most

effective treatments is by means of olive oil, two or three tablespoons taken warm before eating.

*Erosions and Fissures* have about the same symptoms and are treated in about the same manner as gastric ulcers.

*Cancers of the Stomach. Symptoms.*—Insidious onset, loss of appetite, with special repugnance against meat, great prostration, anemia, cachexia, emaciation. When the cancer is in the end of the esophagus we have difficulty in swallowing; when it is in the pylorus we have obstruction with dilation of the stomach and vomiting. Cancers at the end of the esophagus, called cardia, cause obstruction of the esophagus like those at the end of the outlet of the stomach or pylorus, but when they occur in the body of the stomach, say at the lesser or greater curvature, they do not produce obstruction. Thus we have three types: (1) cancers of the cardia with obstruction of the esophagus and difficult swallowing, impossibility to pass the stomach tube; (2) cancers of the pylorus causing stagnation of the contents, vomiting, dilatation; and (3) cancers in the extraostial parts of the stomach causing no obstructions. When a tumor is palpable in the stomach it is as a rule a cancer. In both cancers and ulcers blood is present in the stools. When blood is vomited from an ulcer it is usually bright red, but when it is vomited from a cancer it is usually a dark coffee ground color. The exact diagnosis requires analysis and microscopic examination of the stomach contents and stools.

*Treatment.*—The only successful treatment is by a surgical operation; all other treatments have only a palliative value.

*The Diagnosis of Dilatation, Gastropnoxis, Ulcers and Cancers of the Stomach by Means of X-rays.*—Dilatation as well as gastropnoxis, and according to Hemmeter even gastric ulcer and cancer can be made visible to the naked eye by giving the patient a gruel made of oatmeal containing a heaping teaspoonful of subnitrate of bismuth. When the patient is placed before an X-ray apparatus the bis-

moth cuts off the X-ray and not only can the location and size of the stomach be plainly seen, but after some training and with experience ulcers and cancers can be made visible also. This author was the first clinician to make use of and describe a method to determine abnormal states of the stomach by means of the X-rays (see *Boston Medical and Surgical Journal*, June 18, 1896). At first this method was used only to ascertain the size and location of the stomach. But in 1906 the author published his experiments and observations that resulted in a technique for diagnosing gastric ulcer and carcinoma by the X-ray (see *Archiv für Verdauungs krankh*, BXII, 1906, p. 357.).

*Symptoms.*—Copious vomiting, especially vomiting of food that has been taken one or two days previously. Some patients force the vomiting by tickling the throat with their fingers in order to be relieved of the boring cramp-like pains in the pit of the stomach, which just as is the case with gastric ulcer does not cease until the stomach is evacuated. In addition such patients suffer from heartburn (pyrosis) fullness, distension of the abdomen; the appetite may be good but the patients are afraid to eat because of the distressing consequences. The secretion of urine is very much reduced. Sometimes not more than four to five hundred c.c. in twenty four hours.

*Objective Signs and Symptoms.*—Very low position of the greater curvature of the stomach, gastric peristalsis visible through the abdominal walls running from the cardia to the pylorus. This is absolute proof of the existence of a stenosis or obstruction. The presence of remnants of food gained from the fasting stomach before breakfast by means of the stomach tube is a sure proof of the existence of a dilatation. In benign dilatations hydrochloric acid is always present in the test-meals; generally there is an excess of it; hyperchlordria and hypersecretion are in this case a consequence of the irritating condition at the outlet of the stomach.



When the obstruction is malignant, *i.e.*, if it is due to a cancer, the hydrochloric acid secretion is lost and in the stagnating masses in the stomach we find only such abnormal acids as are produced by the fermentation of food, especially lactic acid.

*Prospects of Cure. Prognosis.*—Whether a dilatation of the stomach will be recovered from or not depends upon the cause. If it is a benign obstruction, such as ulcer of the pylorus or of the duodenum, erosions, fissures, perigastric adhesions, adhesions emanating from the gall bladder and caused by gallstone disease (pericholecystitis), epigastric, hernia, trauma, then the dilatation is curable, although a successful treatment may require an operation, but if the cause is a cancer we can hope only for a prolongation of life by surgical treatment.

*Treatment.*—Even where the cause is a cancer an operation should be undertaken if the general condition of the patient permits it. Cases are on record that have gotten along well for four, six and eight years after the operation. Cases of dilatation of the stomach not due to cancer are treated by operation also when the other bloodless means of treatment do not succeed promptly. Ulcers, fissures and erosions of the pylorus and the consequent spasm of the pylorus with dilatation of the stomach can be cured by purely medical dietetic and mechanical treatment, and one need not resort to surgical operation as long as the patient shows the slightest improvement and gain of weight. The stomach can be washed out daily through the stomach tube and freed of its fermenting masses. This must be done before breakfast. The diet should be so finely prepared that it can be poured through a sieve having openings no larger than the thickness of a darning needle. Thus, boiled milk, raw eggs, soup made of milk, flour and eggs, scraped beef, bouillon thickened with egg and farina or rice, gelatines with wine; in short, all foods that can pass a constricted portion of the pylorus without irritation. When there is excess of HCL acid one hundred c.c. of warm olive oil poured into the stomach after

washing it out acts beneficially in arresting this excessive secretion. The intragastric application of the faradic current is also a valuable adjuvant in the treatment. If after a month of non-surgical treatment there is no improvement the patient should submit to an operation. As the stomach does not absorb water all diseases associated with weakening of the musculature of the stomach should be treated by exclusion of water from the diet as far as possible. In extreme cases the necessary water can be given in form of enemas injected through the colon tube, and the patient quench the dryness of the mouth by swallowing crushed ice. Abdominal bandages, if properly applied in the reclining posture, are a great help in the treatment of dilatation and gastropnoia.

*Gastropnoia, Displacement of the Stomach, Gastric Atony.*—The displacements of the abdominal organs in their relation to diseases of the digestive tract were first thoroughly appreciated in a study by Glenard, and he also correctly emphasized that many so-called purely nervous diseases of the stomach were traceable to these displacements. Stiller thereafter described the so-called *enteroptotic constitution* (*habitus enteroptoticus*); by this is meant an inherited weakened constitution, especially an infirm nervous system. This type of human being Stiller designated as the type *asthenia universalis congenita*. This condition of congenital nervous infirmity is frequently associated with a long, flat, narrow chest or thorax. Stiller has also called attention that the tenth rib in such cases is not attached to the arch of the rib cartilages, but floats about loosely, its end not being held to the ninth rib by any union whatsoever. Another sign of importance has been called attention to by Hemmeter; it is the so-called *sub-xiphoid angle*. The xiphoid cartilage is the tip of the breast bone and the angle which the edges of the short ribs make with this xiphoid tip is the *sub-xiphoid angle* measured with a graduated sector; this angle should be from 100 to 140 degrees in normal individuals, but if the *habitus enteroptoticus* exists it may be

only 60 degrees, or even less. Hemmeter has taken measurements of the entire body in various directions in many hundred normal and diseased individuals, and when there is a *sub-xiphoid angle* of 70 degrees or less he finds that the stomach and the right kidney are invariably displaced downward, and sometimes other abdominal organs displaced at the same time. All of these relations of the bony frame of the entire body as studied in connection with universal neurasthenia and displacements of the abdominal organs indicate that gastropotosis and enteropotosis are not diseases *per se*, but rather they are accompaniments of an inherited weakened state of the entire body, especially of the nervous and digestive system. All patients suffering with gastropotosis or enteropotosis have a vertical diameter of the chest, which is longer than the transverse diameter. Normally the transverse diameter is decidedly the greater. It must be apparent that if the chest is elongated and compressed from side to side in this manner that the abdominal organs immediately beneath the diaphragm must be displaced downward. In a large proportion of these cases the heart is also displaced downward, the aortic arch is drawn out (penulous heart).

*Symptoms.*—Owing to the congenital irregularities of the test formation the stomach which should normally occupy a more or less horizontal position in the upper abdomen are forced to assume an unnatural vertical position. Anything that weakens the abdominal muscles will, of course, aggravate the displacements already existing. Anything that weakens the nervous system acts in the same manner. Gastropotosis can be acquired as well as congenital, and those cases who acquire it in latter life need not necessarily be at the same time afflicted with universal neurasthenia, but all cases that are congenital invariably have this neurasthenia.

*The Subjective Symptoms.*—Consists of the most varied dyspeptic difficulties: there is no complaint conceivable to the human mind which sufferers of that type, do not

at one time or another give expression to. At the same time actual pain in the stomach is a very rare complaint. The most frequent statements given are those describing distension, fullness and oppression in the stomach; certainly after large meals, but in severe cases after any food whatsoever. There is no food in the whole range of human diet which at one time or another does not give rise to distress in such a patient. In addition they suffer from regurgitation, eructation, nausea, loss of appetite, constipation, incapacity for work.

*The Objective Symptoms* consist of emaciation anemia, sharp xiphoid, floating tenth rib, very much relaxed abdominal walls. On distending the stomach with a mixture of sodium bicarbonate, followed by tartaric acid, one teaspoonful of each in a half tumbler of water (it is advisable to drink the tartaric acid first), or on showing up the stomach by means of the X-ray it is found that these displace downward. Sometimes it may be located below the navel, at times the kidney, the liver, the spleen and the transverse colon are displaced downwards at the same time.

*Treatment.*—The use of corsets or of belts should be prohibited; a well-fitting abdominal bandage should be applied in the horizontal position with the hips elevated by several pillows. The iron of the blood should be increased, everything that tends to strengthen or fatten the patient should be done although it gives very much dyspeptic distress in the first two or three weeks. The use of electricity and stimulating baths are followed by good results. No cast iron hard-and-fast dietetic rules should be laid down. Such patients should almost eat whatever they please to eat avoiding naturally such things which common sense tells them is indigestible.

*Nervous Dyspepsia.*—This condition has much in common with the anemic enteroprotic dyspepsia which has been described in the preceding; in purely nervous dyspepsia, however, we do not find the habitus enteroproticus or the enteroprotic constitution, described in the preceding. The for-



mation of the chest and abdomen is, on the contrary, normal, they are not so emaciated or anemic as the gastropstosis cases. The xyphoid angle is generally normal and rarely under 80 degrees.

*Neuroses, Nervous Diseases of the Stomach.*—This group comprises, by far, the largest number of diseases that can befall the human subject, and they are of very difficult recognition, particularly when they are associated with typical organic diseases of the stomach or other organs. Those nervous diseases of the stomach which are associated with the enteroptotic constitution can be recognized by the objective signs described in the articles on gastropstosis and enteroptosis. Every subject that has these physical signs has a congenital infirmity of the central nervous system, and some neuroses of the stomach.

*Classifications.*—There are mainly three groups of gastric neuroses: (1) Those that befall the motility or contractile force of the organ; these are the neuroses of peristalsis. (2) Sensory neuroses. (3) Neuroses of secretion; then there is an illy defined nervous affection of the stomach, which may exhibit signs and symptoms of all three of these groups. This is called neurasthenia gastrica.

Among the secretory neuroses is a curious abnormality first described by Hemmeter, and since then his discovery has been confirmed by Professor Boas of Berlin and his pupils. This disease is characterized by extreme variations in the quantity and quality of the secretion of the gastric juice. After the identical test-meals these observers have found in the same patient and on the same day in some analyses marked excess of HCL and pepsin, and at other times entire absence of these constituents. Under such conditions one of course never knows what remedies to administer to relieve the patient because it is impossible to foretell whether he has an excess or a lack of HCL and ferments. As there is no change in the structure of the stomach in this disease the

entire treatment must be directed toward the nervous system by making use of the sinusoidal electric current or the galvanic current along the spine of the patient and over their region of the stomach. Electrical baths—massage—life in the country, mountains or seashore, abstention from all kinds of mental work, all kinds of excesses, tobacco and alcohol, freedom from business and family cares. These lines of treatment are applicable to all neuroses and, as a detailed description of the diagnosis treatment would lead us too far, we refer the reader to the articles on electrotherapy, hydrotherapy, massage, diet and climate, and conclude this article by giving simply a scheme of the classification of neuroses.

*Neuroses of the Stomach.*—Gastric neuroses may be classed as follows:

- I. Motor.
  - II. Sensory.
  - III. Secretory.
- Under each of these we may distinguish
- (a) States of excitation.
  - (b) States of depression by nervous influences.
- I. Neuroses of motility or peristalsis.
- (a) Irritative states:
    - (1) Cramp of the cardia or cardio spasm.
    - (2) Cramp of the pylorus or pyloric spasm.
    - (3) Cramp of the entire musculature or gastro spasm.
    - (4) The peristalsis unrest of kussmaal.
    - (5) Nervous eructation.
    - (6) Nervous vomiting.
  - (b) Depressive states:
    - (1) Insufficiency of the cardia, including rumination and regurgitation.
    - (2) Insufficiency of incontinence of the pylorus.
    - (3) Atony or insufficiency of the entire gastric musculature (gastroplegia).
- II. Sensory neuroses:
- (a) Irritative states:
    - (1) Hyperesthesia.
    - (2) Gastralgia.
    - (3) Bulimia and polyphagia.
  - (b) Depressive states:
    - (1) Acoria.
    - (2) Anorexia.
- III. Neuroses of secretion.
- (a) Heterochylia.
  - (b) Irritative states:
    - (1) Hyperchylia, hyper-, or superacidity.
    - (2) Supersecretion of gastrosuccorrhea gastroxynsis.
  - (c) Depressive states:
    - (1) Hyperchylia or subacidity.
    - (2) Achylia gastrica and anacidity.
- Nervous dyspepsia.  
Neurasthenia gastrica.

## CO-ORDINATION OF DISCIPLINE IN MEDICAL TEACHING.—THE CLINICAL SEMINARY—ITS ACADEMIC ALTRUISM. A SYMPOSIUM ON NUTRITIONAL THERAPY.

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The duty of conscientious physicians and surgeons to keep abreast of the progress in the medical sciences does not meet with punctilious fulfillment in medical schools, where research is not a regular part of the curriculum.

There are only three methods of keeping step with the advancements of medical science:

1. Personal investigation and objective research in the laboratory or clinic, with exact recording of phenomena and data observed, preferably under the guidance of a man who has successfully completed similar research before and who is conversant with the instruments—apparatus—methods and points of inquiry, the difficulties to be avoided and the literature of the subject.

2. Seeking to learn by the experience of others, by attendance upon lectures and presentations given by men who are acknowledged to be thoroughly familiar with their special field of endeavor, reports of abstracts from articles in medical and scientific journals. Here is the proper field for a medical-journal club.

3. Conferences limited to the discussion of special topics and introduced by one or two persons who have prepared a scheme restricting the reports to a well-defined practical or scientific territory, so that diffusiveness and unnecessary expansion be avoided, and the mental energy be concentrated wherever possible upon one single and simple problem.

This is the proper function of a seminary in the

sense as it is employed by German universities.

There should be regular annual reports by every teacher or instructor, presented in writing to the board of instruction, giving the subject-matter of what he teaches in form of synopsis, the hour of lecturing or conferences, the number of hours of laboratory work and the scientific territory covered.

By such a system the various members of the board of instruction would keep informed concerning the manner and matter of didactic and laboratory discipline in other departments, but this would not necessarily bring them abreast of the progress of these other departments. For what often impresses a teacher as new and valuable in other special sciences is not in reality new, but has been ascertained long ago and which he has not had opportunity or failed to become familiar with.

It is a very frequent and a damaging defect in medical discipline that each teacher revolves almost exclusively in his own narrow little circle. To a certain extent this is unavoidable and perhaps even necessary, for specialization means concentration of energy on a restricted cultural domain.

If, however, specialization proceeds so far as to isolate the teacher from the other disciplines in medicine, he must unavoidably, although perhaps unconsciously, become an ineffective teacher, because his very specialization and isolation has not only estranged him to other branches of med-

icine, but has accustomed him to attribute an exaggerated importance to the small field he has succeeded in mastering (assuming that he has acquired a real mastership in it).

There is a very distressing lack of co-ordination of medical discipline not only in the University of Maryland, but in most all American universities, for men who are very capable in their own line of endeavor—clinical or purely scientific—confess a woeful ignorance concerning the fundamental facts of correlative branches of medical knowledge.

As the various component sciences of medicine grow and expand this discrepancy will become more and more evident, and even now it is a very serious problem of how to ameliorate it.

To my understanding the gaps between different co-ordinate branches cannot be obviated entirely, but much can be done to reduce the degree of individual separation.

One way is by way of a SEMINARY, in which such problems are discussed as bringing into play the minds of men trained in both the pure and applied sciences of which medicine is composed. Such a seminary needs the utmost academic loyalty on the part of the teachers of the University. A purely egotistical man, one who is content to revolve in his own narrow orbit, whose connection with the University is conditioned only by the benefits that accrue to him personally, will not make a helpful seminarian, for in a clinical seminary the guiding principle is the "Golden Rule."

This year the problem of treatment by *diet or nutritional therapy* has been selected as the subject around which all teachers could exchange their thoughts in a most fruitful manner. These italicized subjects have already been discussed on Thursdays from 1 to 2:

1. *The Physics and Chemistry of the Various Foods.*
2. *Caloric Values—Isodynamic Equivalents.*
3. *The Physiology of Food.*
4. *Food in Its Relation to Domestic Economics.*
5. *The Pathologic Physiology of Food Effects.*
6. *Diet in Surgical Treatment. Pre- and Post-operative Feeding.*
7. *The Diet in Infancy and Adolescence.*
8. *Food Anaphylaxis and Idiosyncrasies.*
9. *The Techniques of Nutritional Therapy and the Dietetic Comfort.*

## 10. Artificial Nutrition.

- (1) By stomach tube; (2) by rectum, the nutritive enema—composition—technique; (3) by the skin—subcutaneous nutrition.

## 11. Dietetic Cures:

Nutritional Therapy in—

- (a) Pulmonary and Throat Diseases.
- (b) Heart and Vascular Diseases.
- (c) Nerve—Cord and Brain Diseases.
- (d) Digestive Diseases—Stomach, Intestinal, Hepatic, Pancreatic, Splenic.

## 12. The Nutritional Therapy in Diseases Caused by Parasites, Protozoa, Tapeworms, Ascaris lumbricoides, Oxyuris, Tricocephalus dispar, Uncinaria (or Ankylostoma duodenale), Trichina spiralis, Anguilula intestinalis.

## 13. Nutritional Therapy of Acute Infectious Fevers.

The Pathologic Metabolism of Fever.

## 14. Nutritional Therapy of Diseases of Metabolism:

- (1) Of Diabetes Mellitus.

Different Forms of Diabetes.

## 15. Nutritional Therapy of Uric Acid and Diathesis, Gout, Arthritis Deformans, Oxaluria and Phosphaturia.

## 16. Nutrition Therapy of Anemia, Chlorosis, Leukemia, Pseudoleukemia, Basedow's Disease, Myxedema, Addison's Disease.

## 17. Nutritional Therapy of Skin Diseases.

## 18. Nutritional Therapy of Syphilis and Disturbances of the Sexual Functions.

## 19. Nutritional Therapy of Kidney Diseases.

## 20. Nutritional Therapy of Urinary Organs.

## 21. Nutritional Therapy of Gynecologic Disorders.

## 22. Nutritional Therapy of Obstetric Conditions.

## 23. The Pathologic Physiology of Fat Accumulation and Nutritional Therapy of Obesity.

## 24. Nutritional Therapy of the Abnormalities of the Mineral Metabolism; the Disturbances of the Calcium and Iron Metabolism.

There are numerous instructors who are conspicuous by their absence at the regular medical gatherings, and who are never seen at the aca-



demie ceremonies, reunions of alumni, nor at meetings of the board of instruction.

In fact, it would hardly be known that they are connected with the University except for their attendance upon duties for which they are paid or upon functions from which they anticipate a direct or indirect personal advantage. These are the academic "drones," whose doubtful utility seems to be to serve as ballast in the ship of academic progress. But ballast in a ship is really useful for purposes of steadiness. The word "drone" has another meaning than that of an unprofitable sluggard; it also means that which gives out a "grave and monotonous dull sound."

And this is the one thing in which University drones excel. They do little work, but they are often ready to express "dull and monotonous sound" of criticism about those who are doing work and having their shoulders to the wheel.

Let those who are happy in their work not be discouraged by the drones, no matter in how dignified a tone they utter their fault-finding. Crit-

icism is of benefit only when it is constructive, and unless accompanied by feasible recommendations for betterment it were wiser if all criticism were suppressed.

A clinical seminary is an organization of medical workers where the members are primarily actuated by academic altruism and love of culture.

The question, "What good will it do me?" is a secondary one, though personal advantage does come from this kind of an association, because the various members are made conversant with domains of knowledge acquired by others, sometimes at the expense of life's long endeavor. Thereby they gain new insight not only into problems of life not studied by them, but new aspects of and new pleasures in their own scientific acquirements. The seminary meets weekly on Thursdays at 1 o'clock in the nurses' classroom of the University Hospital, and if those of the staff of instructors who will be interested will send their names to the author, they will be kept informed of the subjects under discussion.





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**Anthropometric studies of the osseous Proportions  
of the human Body, with a view to obtaining a  
mathematic expression for Enteroptosis.**

**The Position of the thoracic Organs in Enteroptosis.<sup>1)</sup>**

By

**John C. Hemmeter, M. D. Phil. D. etc.,**

Professor of Physiology and Clinical Professor of Medicine, University of Maryland, Baltimore.

(With 3 figures in text.)

Sonderabdruck aus: Internationale Beiträge z. Pathologie u. Therapie  
der Ernährungsstörungen. Bd. 2. Heft 3.

Redigiert von Prof. Dr. A. Bickel (Berlin).

(Verlag von August Hirschwald in Berlin NW. 7.)

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In anthropometric studies, racial differences are of such telling effect on the measurements that one of the first aims must be to restrict all comparisons, averages, and calculations strictly to individuals of the same race; therefore, Romance nations, Africans, Anglo-Saxons, Lithuanians, Poles and Slavs must be carefully kept apart in the measurements. We have a very mixed population in Baltimore, even Orientals — Japs and Chinese — which were rarely encountered, however.

The degree or size of a definite dimension or measurement oscillates even for the same race, same age, and same sex, between two limits, which may be designated as „maximum“ and the „minimum“ dimensions. These individual variations in the same racial group, whose proportions of mass and extent we are trying to seek, can therefore not be expressed in terms of a simple linear measure.

But nevertheless, there is a certain lawfulness of the anthropometry of the trunk; for instance, if we have settled by a large number of measurements upon what is the „Maximum“ and what the „Minimum“, it is found that every stage of magnitudes lying between these two, occurs with a definite and certain frequency.

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<sup>1)</sup> Read before the American Gastro Enterologic Association at St. Louis. June 1910.



In order to reach an expedient mathematical expression of these human dimensions, W. Pfitzner („Die Proportionen des erwachsenen Menschen“ in *Zeitschr. f. Morphologie u. Anthropologie*, Bd. II, S. 222) has proposed a third basal figure, namely, the middle value between maximum and minimum; this he calls the „Plurimum“.

The magnitude of the „Plurimum“ is then given by the arithmetic, middle value of all cases. And we really find in all of our measurements that for every grade between maximum and minimum, there is a strict lawfulness; that is, from the „Minimum“ upward towards the „Plurimum“, the figures of frequency of every variation increase regularly, step by step and from this point toward the „Maximum“ they decrease regularly, in the same manner. Such measurements, to be anywhere near exact require an enormous clinical material. But I have had the advantage of the help of large classes of medical students who aided on measurements on each other and on other normal individuals, as well as on patients, and tho we have been collecting measurements off and on for ten years, our material still impresses me as insufficient to base accurate deductions upon, but they serve to demonstrate a very promising field of research and to define the needs and methods of the problem.

Pfitzner states (l. c. p. 227) that with a sufficiently large and sufficiently homogenous material, the average of all measurements coincides with the „Plurimum“.

The average deviation of any individual from the dimensions of the „plurimum“ Pfitzner designates as the oscillation exponent (in formula as O. E.). The oscillation exponent is average medial deviation of any individual case from the „Plurimum“ (on either side); it is a measure of the intensity of the anthropometric variation of the individual.

The principal parts of the mammalian body are three: 1. the trunk; 2. the extremities; 3. the head. There are therefore four elements of anthropometry: 1. dimensions of the head: 2. axis length of the trunk; 3. length of axis of arms or cranial extremity; 4. axis length of caudal extremity (legs).

I have taken great care to understand the measurements of Pfitzner and to compare them with our own on enteroptosis, and find that these are entirely irregular in their osseous correlations. They present no normal proportions of dimensions between

the above elements of measurement, as individuals should, that are formed regularly, and they present a large disproportion between body mass and body dimension. If one has, for instance, measured 3000 individuals of the same race and has classed them into three groups, namely, those 1. representing the smallest measurements—minimum, 2. those presenting the largest measurements, i. e., the maximum, 3. those showing the dimensions that occur with average frequency between minimum and maximum, i. e., the „plurimum“, it will be self-evident that the latter will present the largest group of individuals, because those of the maximum and minimum dimensions must „ipso facto“ be the exceptions. It is impossible that out of 3000 measurements, there should be 1000 in each group; it is more likely for example that over 2000 individuals will be found in their measurements to stand somewhere midway between minimum and maximum. Hence the meaning of the word „Plurimum“ — it signifies those dimensions under which a plurality of the individuals measured will be found to accord or fit.

The determination of the minimum and maximum measurements is very indefinite. We must emphasize that outside of enteroptosis cases we aimed only to study normal individuals; this excludes giants, dwarfs, as well as over developed individuals in an athletic sense.

Now supposing that the percentage frequency of occurrence of „maximum“ and „minimum“ individuals is found to be 0,1 pCt. This figure in itself indicates that such individuals can only be found in a material amounting to thousands. In a small material amounting only to hundreds, individuals occurring only with a frequency of 0,1 pCt. will not be found. Therefore, the limits of maximum and minimum must be variable and indefinite and hence would tend to give an impression of insecurity to all of our anthropometric studies. Fortunately the brilliant work of Pfitzner has given a certain stability to our calculations in that he has established that the „Plurimum“ — which is the medium or middle value of dimensions — between „maximum“ and „minimum“, can be ascertained with definiteness and constitutes the most important arithmetic element in the characterization of varying proportions of the human body.

If we were for example to divide the number of individuals from minimum to the maximum into 100 groups, so that there

would be 50 groups on each side of the „Plurimum“, we would find that the frequency of human dimensions in each group is strictly a matter of lawfulness, i. e., that it increases in nearly arithmetic proportion from minimum to „plurimum“; and from this step to the „maximum“, the frequency of certain human measurements decreases again with the same regularity. At either side of the scale or curve the extremes figure may be designated theoretically as (0) zero. Expressed in different terms, I mean this: starting from the centre, i. e., the „Plurimum“, the frequency of individuals of certain dimensions decreases regularly, in perfect agreement toward both sides, the „Maximum“ and „Minimum“. Every group on the minimum side has a corresponding group on the maximum side in exactly the same frequency. The sum of individuals that are smaller than the „Plurimum“ and the sum that are larger, are exactly alike, in each group. Expressed both graphically (in a curve) as well as arithmetically (in figures), this fact remains the same. In a curve the exact spot or location of the plurimum is midway between „Maximum“ and „Minimum“, but expressed in figures, we have the plurimum represented by the middle value of the total number of all cases. Furthermore, each of two corresponding groups of such anthropomorphic material harmonizes in their dimensions to such a degree that a definite group on the minimum side is smaller than the plurimum by the same degree as the corresponding group on the maximum side is larger. They supplement each other, therefore, to form an average which is constant (see Pfitzner, *Zeitschr. f. Morphol. u. Anthropologie*, Bd. V, 1903, S. 223). So that average middle value of all human proportions is the simplest way of determining the „Plurimum“.

#### Anthropometric studies concerning enteroptosis.

The admirable study of Pfitzner (l. c.) has enriched anthropometry by several well established and useful guiding principles. For instance, he laid down the rules establishing the arithmetical average; then he established a constant relation between this average and the oscillation exponent and also the relation between this exponent and the extent of the variations; then he made clear that variations of measurements and variations of proportion are controlled by the same laws. But perhaps the most important addition he made to anthropometry, and one which we must bear

in mind in a study of the proportions of enteroptotics was the finding of a unit of measurement from which all other measurements could be proportioned. This anthropometric unit is the stature or the body length. His measurements, however, were restricted to those of the head, trunk, arms, legs and the stature. There are no measurements of the thorax or the abdomen given in his interesting publications.

It should be stated here, that measurements over the abdomen are all fallacious if they concern only the soft parts, that is, if the entire measurement is around the waist, for instance, for the abdominal wall being distensible by the gaseous solid and liquid contents of the intestines will greatly vary the measurements. I have found that the measurement of the girth, such as is used in the determination of the „Becher-Lennhoff index“ may vary from an inch to an inch and one-half in the same individual in the same day. Measurements taken across the abdomen, therefore, should not be around the girth or the narrowest part of the abdomen<sup>1)</sup>, but from one bony point on the thorax to other bony points that can be readily felt on the bones of the pelvis. For this purpose I have suggested the measurement of a triangle, the apex of which is formed by the tip of the xyphoid cartilage and the base by a line running from one anterior superior spine of the ileum to the other. Thus the measurements would be as follows:

1. From the xyphoid cartilage to the right anterior superior spine.
2. Xyphoid cartilage to left anterior superior spine ileum.
3. From right anterior superior spine to left anterior superior spine ileum.

These measurement, while they unavoidably pass over soft parts, still the beginning and end of the measurement is over as stationary an osseous point as can possibly be obtained on the human frame. The superior spines of the ileum do not move at all when the patient is reclining and the xyphoid can be kept stationary by requesting the patient to hold the breath for a minute. This is also necessary in taking the measurements of the circumference of the thorax. As a unit for the measurement of the length of the thorax, I found that the sternum was the most reliable standard. The first measurement is taken from the top

1) The girth may be the greatest circumference in some individuals and a so called narrowest circumference of the abdomen may not exist.



of the manubrium or interclavicular notch to the tip of the xyphoid. The second from the manubrium to the umbilicus; the third from the top of the manubrium to the symphysis pubis. Then the patient is measured from the atlas to the tip of the coccyx. Where this is not convenient, the measurement from the atlas to the fifth lumbar vertebrae will serve a purpose, provided it is definitely stated in the tabulation. Then the height of the patient is taken, the age, the weight and the sex. What will be found hereafter to be the most important measurement, however, is the infrasternal angle, or as I have called it, the xyphoid angle. It is the angle which the edges of the costal cartilages make with the tip of the xyphoid cartilage.

As a general rule, the lines connecting the tip of the xyphoid cartilage with the r. and l. anterior superior spines of the ileum will form tangents with the costal cartilages, and in normal individuals, thus form the xyphoid angle. This is, however, not always the case. In enteroptotics it is rather the exception than the rule.

The 1126 measurements upon which our studies are based, were all taken on living individuals. When I say that pathological individuals were excluded, I refer only to pathology of the skeleton; enteroptosis cases were placed in a separate group by themselves and compared with individuals who have their viscera in normal position.

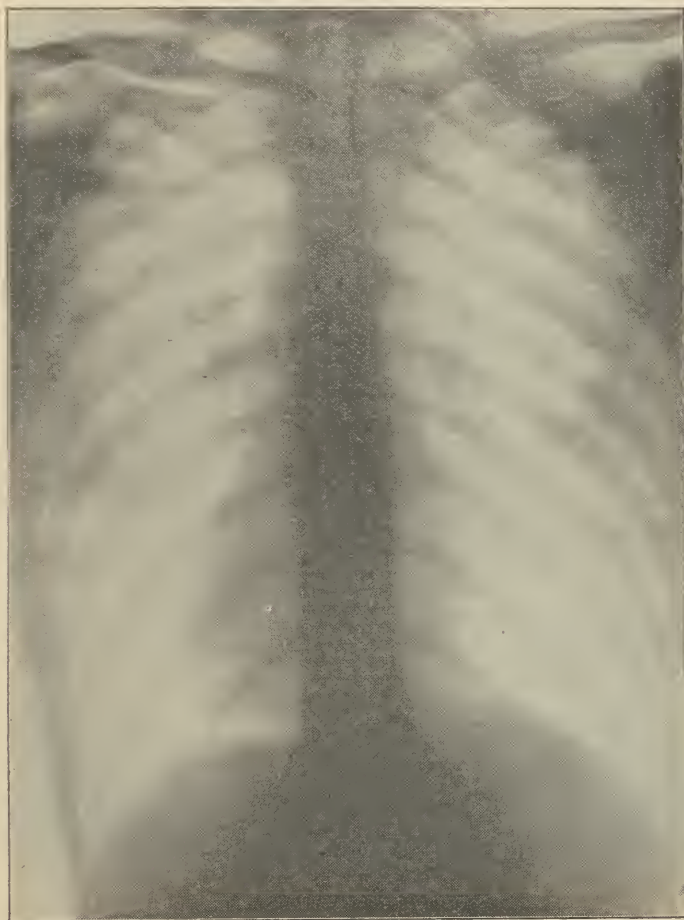
From our tables, which accompany this report, it can be easily ascertained what the normal thoracic and abdominal measurements should be in individuals of certain age, sex, height, weight. Children are not included in these tables because the digestive organs do not attain to their correct and permanent position until the age of puberty has been passed.

#### **The position and dimensions of the organs of the thorax in enteroptosis.**

In all studies concerning enteroptosis that have so far been published, either no special attention has been paid to the position of the thoracic organs, or they have been assumed to be normal in position and dimensions. I have not been able to discover in the entire literature of enteroptosis, a single definite reference that any one of the clinicians or investigators has studied this subject.

The location and size of the heart and lungs and of the aorta can be studied by the approved methods of auscultation and percussion, either singly or both combined; the position and dimensions of the esophagus can be studied by esophagoscopy and

Fig. 1.



Röntgenbild einer Herzverlagerung bei Enteroptose mit Cor pendulum.  
Derselbe Fall — Herr Fred. E. — wie bei Fig. 2 u. 3, wo die Gastropse im  
Röntgenbild gezeigt wird.  
Die rechte Niere und das Colon transversum waren in diesem Falle ebenfalls  
verlagert.  
NB. Durch Reduktion des Formats ist ein photographischer „Situs inversus“  
entstanden.

Röntgen ray photogray after the esophagus has been coated with bismuth or a long deglutable rubber tube has been swallowed, which is filled with bismuth. The dimensions and location of the heart can also be ascertained by radiography and by the ortho-

Fig. 2.



Herzverlagerung bei Enteroptose. Der Magen ist mit einer Aufschwemmung von Calciumcarbonat und Calciumphosphat in Hafergrütze angefüllt. Photographischer „Situs inversus“. Fig. 3 deutet denselben Fall in richtiger Stellung an.

diagraph and by orthophotography (according to Immermann and Lepper). The heart may be photographed by the X-rays 1. in sagittal dorsoventral transillumination, 2. in frontal transillumination,

3. in oblique transillumination. Under the latter, Holzknecbt distinguishes four different positions. 1. oblique transillumination, X-ray (Crook) tube on left shoulder, screen or plate on the right anterior side of the thorax; 2. tube on the right anterior side of

Fig. 3.



Herzverlagerung bei Enteroptose.

Der Magen ist mit einer Aufschwemmung von Calciumcarbonat und Calciumphosphat in Hafergrütze angefüllt. Diese Calciumsalze eignen sich nach unseren Erfahrungen ebenso gut zur Photographie des Magens mit Röntgenstrahlen, wie das Bismut. Sie sind durchaus ungiftig und haben selten Obstipation im Gefolge.

thorax, screen or plate on left shoulder; 3. tube on the right shoulder, screen on left anterior thorax; 4. tube on the left anterior side of the thorax, screen on right shoulder.



The size and location of the heart will differ in each position and therefore it should be stated on every photograph in which position the patient was placed in regard to the parts of the apparatus. In the first position, we have two principal objects dividing three clear fields, a right and left lung field, which should be clear, a middle clear field, and these divided up by two dark fields, one the definite outline of the spinal column and the other the shadow of the heart and aorta. The light middle field has great importance for the esophagus runs through it and if it is desired to make it out in the Röntgen picture, one of the methods already described must be used.

The second direction of transillumination in the reverse or the optical mirror reflection of the first, with this difference; the heart and the vessels lie nearer to the tube and therefore appear larger and less well defined. In the third direction there is no clear middle field, for the heart with its left chamber projects into this field on the left side. The fourth oblique direction of transillumination has the least diagnostic significance because the heart is much magnified, poorly defined, and obstructs the shadow of the other contents in the thorax.

There are three difficulties in the way of absolutely exact deductions from Röntgen rays photography of thoracic and abdominal organs and these apply also to orthodiagraphy. These are 1. the personal equation, that is, the artistic versatility and experience of the observer; 2. the accuracy and technical perfection of the apparatus; and 3. the error that may arise from drawing a conclusion from projection, that is, from calculating a volume out of a surface magnitude. Then again the heart changes with every systole and diastole. The effect of inspiration and expiration on the radiography can be partially prevented by directing the patient to hold the breath; but even with all precautions, we get the silhouette of the heart in its diastolic position, this being the largest shadow that is thrown and there is generally a linear error of at least 4 or 5 millimetres.

Most of our radiography was done by Dr. Howard E. Ashbury at the University of Maryland and the Hebrew Hospital, where the most modern apparatus for this purpose has been provided.

With all these methods we found that the heart of the enteroptotic patient is in the large majority of cases not in normal position. The orthodiagraphic method was not used by us but

only simple radiography combined by percussion and auscultation. It is evident from a few of the plates which we will reproduce in this article, that the hearts of the individuals are not only lower in the thorax than they ought to be, but that the heart is slightly twisted upon itself and rests with the right auricle and ventricle more flatly upon the diaphragm, the apex pointing more directly towards the left. It is evident that in such a position as this, the heart draws upon the great vessels and that they are inevitably elongated.

The lungs do not constitute favorable organs for radiography unless they are rendered more solid by abnormal conditions and enlargements of the peribronchial glands; therefore, percussion and auscultation together with measurements of the thorax, constitute a better method of ascertaining the location and dimensions of the lungs. The spirometer should be used in connection with this method in order to ascertain the capacity and the figures for tidal, complemental, supplemental, air and vital capacity. It has impressed itself upon me that the enteroptotic patient has a lung that does not extend as far upwards under the clavical as it does in the normal individual. This is probably explained by the tugging upon the bronchial tree that must be exerted through the large pulmonary vessels as they are dragged downward by the displaced heart. (W. Scott Halls chest Pantograph was found of value to ascertain the Contours of the thorax.)

I must emphasize here, in agreement with Moritz, that the heart descends deeper towards the abdomen in the vertical position than it does in the horizontal position. Therefore, photographs taken in these two positions cannot be compared as identical. There is an orthodiagraph in which the patient can be photographed in both positions; this has still further been improved by Franz M. Groedel by a device through which the patient can be completely fixed in a definite position and that the drawing of what is seen can be outlined on a surface placed between the observer and the patient.

That the esophagus is elongated should not surprise us in enteroptotic when we may conclude from our figures that the entire thoracic skeleton is elongated also, but the chief point to bear in mind is, that enteroptosis is not an abnormality limited exclusively to displacements of the abdominal viscera, but that the thoracic organs are also displaced

as far as the diaphragm and the osseous limitations of the thorax will permit it.

**Enteroptosis as a general osseous, visceral, nervous and vasomotor abnormality.**

In my text-book on „Diseases of the Stomach“ and „Diseases of the Intestines“ (P. Blakistone's Sons & Co., Pub., Phila.) I have long ago sided with those authors who conceived enteroptosis in the large majority of cases to be what has been called a constitutional abnormality and that it rests upon an inherited disposition. The cases that are acquired are disappearingly small in number and then only show displacements in a few organs of the abdomen.

I wish to emphasize this as a distinction between the rare cases of acquired enteroptosis and the more frequent cases of congenital enteroptosis (or inherited); that in the acquired form, the thoracic organs are as a rule, in normal position and the osseous anthropometric proportions of the body are not found to be deviating from the normal in the acquired form. In the inherited, and more frequent type, the thoracic organs are rarely in normal position, there are always several abdominal organs out of position and the osseous proportions are decidedly abnormal.

To Stiller is due the credit of having first recognized and appreciated that enteroptosis is an abnormality on a constitutional basis and is associated with a distinct infirmity of the entire nervous system and a distinct irregular build of the osseous architecture of the thorax. (Stiller, Ueber Enteroptose etc. Archiv für Verdauungskrankheiten. Bd. II. Heft 3.) Also, (Stiller. Die asthenische Konstitutionskrankheit. Stuttgart 1907.)

Hitherto there has been only one mathematic index proposed for enteroptosis, the Beecher-Lennhof index for (asthenia universalis congenita). This is obtained by dividing the distance of the jugulum from the upper edge of the symphyses by the number expressing the smallest circumference of the abdomen and multiplying the quotient by 100. It is a purely empirical proceedure and has given no results that could be called even approximately reliable. The unreliability of the average of this index which for the normal female body in dorsal position is 75, is that one of the factors is extremely variable, namely, the abdominal circumference. This may vary 4 to 5 cm in the same individual on the

same day, according to the distention of the stomach and intestines by food, gas, feces etc.

For males, the average of this Beecher-Lennhof index is less than 75. A high index, over 80, is found in persons with palpable kidneys and the asthenic enteroptotic constitution. Before we know that Beecher and Lennhof had proposed it, we had already tried it and discarded it because of its extreme variations in normal persons.

Concerning the floating tenth rib which Stiller proposed as a stigma that, as he claimed, was pathognomic for enteroptosis (*Costa decima fluctuans*), much has been written. It occurs in my records in 75 pCt. of the cases of enteroptosis. It is necessary to distinguish between a movable 10th rib and an entirely detached 10th rib. Stiller did not assure himself whether the 10th rib was always normally firmly attached to the costal arch.

Tandler (*Wiener klin. Wochenschr.* 1900. No. 8. S. 200) and Meinert (*Wiener klin. Wochenschr.* 1900. No. 2) that a loose 10th rib is rather the rule than the exception and actually represents the normal condition.

The reason it is so readily felt in enteroptosis is — the usual marked elongation of the thorax with a narrowing of the lower part and the usual emaciation of these patients. Any persistent narrowing of the lower thorax must eventually force away the 10th rib from its costal attachment.

I regard enteroptosis as a pathologic interbreeding product of some inferior race that has become engrafted upon the Caucasian race and is now perpetuated by heredity. Among the Arian races the enteroptotics constitute a hybrid or under-race. Hybrid, from the Greek *ἕβρις* — wantonness, lawless — produced from a mixture of two species, i. e., a superior and inferior species (see Pfitzner, p. 217, l. c.). Far back in the history of the race it may have been acquired by part of the race during prolonged migrations, marches, wars and exposure to handship-compulsory vertical position for long periods.

Enteroptosis is only exceptionally acquired; it is in most cases congenital and as so many congenital osseous, psychic and temperamental irregularities are present in the same individual, I conceive the hypothesis that they are a special variation of the human race. Three times have I observed three generations in the same family, all enteroptotic.



Compilation of 810 cases females.

Anthropometric proportions in relation to enteroptosis. (Female.)	Height in feet										
	5'	5' 3"	5' 4"	5' 5"	5' 6"	5' 7"	5' 8"	5' 9"	5' 10"	5' 11"	5' 11½"
M to X (Means distance from the manubrium to the xyphoid cartilage) . . . . .	162 <sup>2</sup> / <sub>3</sub>	1711 <sup>1</sup> / <sub>18</sub>	19	18	18	19	19	20	21	21	22
M to U (Means the distance from the manubrium to the umbilicus) . . . . .	314 <sup>1</sup> / <sub>9</sub>	321 <sup>1</sup> / <sub>9</sub>	324 <sup>1</sup> / <sub>11</sub>	33	33	34	34	35	36	38	40
M to S (Means the distance from the manubrium to the symphysis) . . . . .	48	497 <sup>1</sup> / <sub>9</sub>	503 <sup>1</sup> / <sub>11</sub>	54	53	52	53	53	54	56	57
X to RAS (Means the distance from the xyphoid to right superspine ileum) . . . . .	265 <sup>1</sup> / <sub>9</sub>	27	25	28	28	27	29	30	30	30	31
X to LAS (Means the distance from the xyphoid to left superspine ileum) . . . . .	272 <sup>1</sup> / <sub>9</sub>	2613 <sup>1</sup> / <sub>18</sub>	27	27	28	27	28	31	30	29	30
R to LAS (Means the distance from right to left anterior and superior spine ileum) . . . . .	245 <sup>1</sup> / <sub>9</sub>	255 <sup>1</sup> / <sub>9</sub>	25	28	27	27	28	30	30	30	31
Circum at X (Means circumference at xyphoid) . . . . .	658 <sup>1</sup> / <sub>9</sub>	687 <sup>1</sup> / <sub>9</sub>	68	67	66	67	70	71	73	74	76
Atlas to 5 Lumbar . . . . .	581 <sup>1</sup> / <sub>9</sub>	582 <sup>1</sup> / <sub>9</sub>	56	66	65	66	69	70	71	72	75
Height (in centimeters) . . . . .	152.4	160.0	162.5	165.0	167.6	170.1	172.7	175.2	177.7	180.3	182.8
Weight (pounds) . . . . .	1102 <sup>1</sup> / <sub>9</sub>	125 <sup>1</sup> / <sub>2</sub>	121	119	135	125	135	144	150	150	160
X-Angle (Means the angle below the xyphoid. Infra sternal) . . . . .	66	68	68	69	69	70	70	72	73	73	75

The average (plurimum) dimension of the infra xyphoid angle in normal females varies with the height (stature) and age.

The average normal female xyphoid angle at an age of 30 and stature of 5 feet or 152.4 cm is 80.2 degrees (318 measurements).

Compilation of 315 cases of males.

Anthropometric proportions in relation to enteroptosis. (Male.)	Height in feet												
	5'	5' 1"	5' 2"	5' 3"	5' 4"	5' 5"	5' 6"	5' 7"	5' 8"	5' 9"	5' 10"	5' 11"	5' 11½"
M to X (Means distance from the manubrium to the xyphoid cartilage) . . . . .	18	19	19	19	20	20	20	21	22	23	23	24	24
M to U (Means the distance from the manubrium to the umbilicus) . . . . .	32	32	34	34	34	34	35	36	36	38	38	39	40
M to S (Means the distance from the manubrium to the symphysis) . . . . .	50	51	51	50	52	53	53	54	54	56	57	59	60
X to RAS (Means the distance from the xyphoid to right superspine ileum) . . . . .	27	27	28	28	28	28	29	29	30	31	32	32	32
X to LAS (Means the distance from the xyphoid to left superspine ileum) . . . . .	26	27	28	27	28	27	29	30	30	30	31	32	33
R to LAS (Means the distance from right to left anterior and superior spine ileum) . . . . .	27	27	27	28	27	28	28	30	30	30	31	32	33
Circum at X (Means circumference at xyphoid) . . . . .	69	70	73	72	74	76	76	77	78	80	79	80	80
Atlas to 5 Lumbar . . . . .	66	68	69	69	70	70	71	73	73	75	75	76	78
Weight . . . . .	130	136	155	131	133	153	140	146	150	150	170	170	180
X-Angle (Means the angle below the xyphoid. Infra sternal) . . . . .	68	69	69	69	70	71	72	73	73	74	75	75	76
Height in centimeters . . . . .	152.4	154.9	157.4	160.0	162.5	165.0	167.6	170.1	172.7	175.2	177.7	180.3	182.8

The measurements are in the metric system (meters and centimeters). The angle is expressed in degrees of a right angle. The weight in pounds.

The average (plurimum) of the infra xyphoid angle in males varies with the stature and age. At age of 30 years and at a stature of 5 feet or 152.4 cm the average male infra xyphoid angle is normally 84° degrees (320 measurements).

Anthropometric proportions in relation to enteroptosis. (Male and female.)																
	Mrs. S.	Mrs. J. G.	Mrs. L. E. C.	Mr. C.	Mr. M. R.	Mrs. S.	Mrs. S.	Mrs. P.	Miss E. H.	Mrs. X.	Mr. R. A.	Mr. P.	Mrs. H.	Mr. J. R. W.	Mr. H. J. E. V.	Mr. W. O. F.
M to X (Means distance from the manubrium to the xyphoid cartilage)	15	17	20	16	22	18	16	21	18	15	16	17	17	20	21	22
M to U (Means the distance from the manubrium to the umbilicus)	34	27	37	32	41	35	32	32	35	23	31	34	35	35	38	39
M to S (Means the distance from the manubrium to the symphysis)	45	52	56	44	56	52	44	45	51	50	49	50	49	50	59	56
X to RAS (Means the distance from the xyphoid to right supraspine ilium)	30	31	30	26	32	29	27	20	29	31	28	29	29	32	29	32
X to LASS (Means the distance from the xyphoid to left supraspine ilium)	29	32	31	26	32	28	27	20	28	31	29	29	29	31	29	31
R to LASS (Means the distance from the right to left anterior and superior spine ilium)	27	25	28	20	26	27	20	20	23	22	27	20	29	28	23	29
Circum at X (Means circumference at xyphoid)	73	65	84	55	82	59	55	57	67	73	70	76	76	76	77	80
Atlas to 5th Lumbar	60	62	60	62	60	59	64	54	59	59	57	59	56	54	70	68
Height (in centimeters)	152.4	152.4	154.9	157.4	157.4	160.0	162.5	165.0	167.6	167.6	170.1	162.7	175.2	177.7	180.3	185.4
Weight	108	102	110	108	—	104	90	114	110	130	120	130	125	138	133	160
X-Angle (Means the angle below the xyphoid. Infra sternal)	45	35	60	48	56	33	48	40	42	35	60	38	68	60	54	68

A list of seventeen measurements in enteroptosis — 8 females — 9 males arranged according to height on stature. Note that increase in stature does not necessarily imply increase in weight or sub xyphoid angle. Age of individuals = between 30 and 40 years.

Anthropometric proportions in relation to enteroptosis. (Female.)	Mrs. G.	Mrs. C.	Miss M.	Mrs. J.	Mrs. R.	Miss P.	Mrs. E.	Miss C.	Miss M. J.	Miss P.	Miss E.	Mrs. R.	Mrs. E. Z.	Miss L.	Miss L. C. H.	Mrs. C. M. D.	Mrs. H.
M to X (Means distance from the manubrium to the xyphoid cartilage)	15	19	18	16	20	15	19	19	18	19	19	20	16	19	15	20	19
M to U (Means the distance from the manubrium to the umbilicus)	34	32	26	32	32	33	33	37	33	26	34	33	36	32	34	36	40
M to S (Means the distance from the manubrium to the symphysis)	45	47	48	48	45	50	51	53	45	54	51	49	52	50	51	55	52
X to RAS (Means the distance from the xyphoid to right supraspinal ileum)	30	23	25	27	23	27	29	27	27	26	29	27	29	25	30	33	25
X to LASS (Means the distance from the xyphoid to left supraspinal ileum)	29	24	25	29	24	27	28	26	27	26	28	26	29	24	29	32	25
R to LASS (Means the distance from the right to the left anterior and superior spine ileum)	24	22	23	23	24	24	23	25	25	22	23	22	24	23	26	25	24
Circum at X (Means circumference at xyphoid)	73	56	77	61	64	67	81	74	66	69	68	66	79	64	73	70	70
Atlas to 5th Lumbar	60	53	60	61	53	54	51	68	58	60	61	68	67	62	61	69	70
Height (in centimeters)	152.4	152.4	160.0	160.0	160.0	160.0	162.5	162.5	165.0	167.6	170.1	170.1	170.1	170.1	170.1	172.7	182.8
Weight	115	110	125	118	110	115	130	117	110	110	130	102	135	105	140	138	140
X-Angle (Means the angle below the xyphoid. Infra sternal)	45	46	60	60	65	46	58	62	68	60	68	50	60	60	42	50	64

Seventeen female cases arranged according to height or stature.



Anthropometric proportions in relation to enteroptosis. (Female.)	Mrs. C.	Miss K.	Miss J.	Mrs. P.	Miss P.	Mrs. L.	Mrs. R.	Miss A. M.	Mrs. L.	Miss R.	Mrs. B.	Miss W.	Mrs. C.	Mrs. D.	Miss M. J.	Mrs. H.
M to X (Means distance from the manubrium to the xyphoid cartilage) . . . . .	16	16	16	19	19	17	20	18	16	20	19	17	23	23	18	19
M to U (Means the distance from the manubrium to the umbilicus) . . . . .	32	30	32	35	26	33	33	32	29	32	36	33	37	38	33	20
M to S (Means the distance from the manubrium to the symphysis) . . . . .	50	47	48	54	54	47	49	48	47	45	50	46	53	56	45	52
X to RAS (Means the distance from the xyphoid to right superior spine ileum) . . . . .	26	26	27	26	26	28	27	25	25	23	29	25	27	27	24	25
X to LASS (Means the distance from the xyphoid to left superior spine ileum) . . . . .	26	27	29	26	26	28	26	25	25	24	28	26	26	27	24	24
R to LASS (Means the distance from the right to the left anterior and superior spine ileum) . . . . .	24	22	23	22	22	27	22	27	24	24	26	23	25	25	27	24
Circum at X (Means circumference at xyphoid) . . . . .	79	75	61	69	69	55	66	77	64	67	73	71	74	75	66	70
Atlas to 5th Lumbar . . . . .	58.5	59	61	60	60	50	68	60	—	53	63	55	68	57	54	70
Height (in centimeters) . . . . .	157.4	157.4	157.4	167.6	167.6	170.1	170.1	172.7	172.7	172.7	173.9	177.7	180.3	180.3	182.8	182.8
Weight . . . . .	109	108	106	110	110	122	102	130	132	132	128	126	117	130	110	—
X-Angle (Means the angle below the xyphoid. Infra sternal) . . . . .	60	55	48	60	60	66	48	60	55	64	58	55	62	65	68	64

Measurements of 16 cases of enteroptosis in females.

Arranged according to stature.

The Darwinian theory of descent, forces itself in at this consideration as well as the question of the „survival of the fittest“. This is not the proper place to enter upon the question as to whether acquired characteristics can be transmitted by inheritance or not (Weissman). Or whether natural selection can explain the endurance of a pathologic type of the human race and even its increase in number.

Certainly the term „survival of the fittest“ is not applicable to these individuals for they are entirely „unfit“, and still their type is seen more and more frequently.

The idea of „Pedogenesis“ suggests itself here, i. e. arrest of development of certain organs at a foetal or at least infantile stage. Also „Heterogenesis“ or the production of forms differing essentially from the parents.

But these terms are nothing but designations for helpless hypotheses.

Two questions of intensest interest remain unsolved:

A. How could such types of 1. partial or complete displacement of the thoracic and abdominal organs 2. of disproportion in the osseous stature 3. of infirm nervous function originate? And secondly:

B. Why is it that such a complication of abnormalities continues and even multiplies through the race?

Experimentally nothing can be accomplished to investigate this problem, for the aim would have to be, to test whether such types of beings could be produced artificially, and as there are no obtainable animals that habitually walk erect (excepting the rare „*Pithecanthropos erectus*“ of Java (first described by the Dutch military surgeon, Eugene Dubois, Batavia 1894) the problem offers unsurmountable technical difficulties.

Human embryology and anthropology, however, do still offer promising aspects of scientific enquiry concerning enteroptosis combined with disproportion of the bones abnormal nerve function, and vascular tonus.

#### Abstract.

Anthropometric studies of the osseous proportions of the human body, with a view to obtaining a mathematic expression for enteroptosis.

In anthropometric studies only the dimensions of the same race are to be compared. Even for the same race, age and sex,

the degree or size of a definite dimension oscillates between two limits, viz., a) the Maximum, and b) the Minimum.

It is found that every stage of magnitude of human dimensions between these two extremes occurs with a definite frequency when a sufficiently large material is measured. A third basal figure midway between maximum and minimum is proposed, and in accordance with Pfitzner, used as the general average dimension; this is the „Plurimum“. The oscillation exponent represents the average medial deviation of any individual case from the dimensions represented by the „Plurimum“; it is a measure of the intensity of the personal variation of each individual — that which distinguishes him from the measurements of the „Plurimum“.

There are four mathematic basal dimensions: those of 1. the head, 2. axis length of the trunk, 3. length of axis of arms or cranial extremity, 4. length of axis of caudal extremity (legs).

Starting from the centre, i. e., the „Plurimum“ the frequency of individuals of certain dimensions decreases regularly, in perfect agreement toward both sides, the „Maximum“ and „Minimum“. Every group on the minimum side has a corresponding group on the maximum side in exactly the same frequency. The sum of individuals that are smaller than the „Plurimum“ and the sum that are larger, are exactly alike. Expressed both graphically (in a curve) as well as arithmetically (in figures), this fact remains the same. In a curve the exact spot or location of the „Plurimum“ is midway between „Maximum“ and „Minimum“, but expressed in figures, we have the plurimum represented by the middle value of the total number of all cases. Furthermore, each of two corresponding groups of such anthropometric material harmonize in their dimensions to such a degree that a definite group on the minimum side is smaller than the plurimum by the same degree as the corresponding group on the maximum side is larger. They supplement each other, therefore, to form an average which is consistent (see Pfitzner, *Zeitschr. f. Morphologie u. Anthropologie*, Bd. V., 1903, S. 223). So the average middle value of all human proportions is the simplest way of determining the „Plurimum“.

Several well established and useful guiding principles have been laid down by Pfitzner in his study of anthropometry: 1. the rules establishing the arithmetical average; 2. the constant relation between this average and the oscillation exponent and the relation between this exponent and the extent of the variations; 3. the

made clear that variations of measurements and variations of proportion are controlled by the same laws. The most important addition he made to anthropometry, however, was the finding of a unit of measurement from which all other measurements could be proportioned. This unit is the „Stature“ or the body length.

Measurements over the abdomen, if they concern only the soft parts, are fallacious, for the abdominal wall being distensible by the solid and liquid contents of the intestines will vary the measurements. Measurements taken across the abdomen, therefore, should not be around the girth, or narrowest part of the abdomen, but from one bony point on the thorax to other bony points that can be readily felt on the bones of the pelvis. See the conclusions in German.

I desire to express my thanks to Dr. Louis C. La Barre and Dr. Albert H. Carroll for their loyal assistance in taking these measurements.

### Résumé.

I. Vergleiche von Rumpfmessungen, in verschiedenen Richtungen an 1125 Enteroptotikern ausgeführt, ergeben, dass diese Abnormalität durch Disproportionen der Rumpfdimensionen gekennzeichnet ist. Als Normalwerte wurden Pfitzner's (l. c.) Messungen angenommen.

Das ganze Skelett beim ausgesprochenen Enteroptotiker ist disproportioniert, wenn die Maasse desselben mit diesen Normalwerten verglichen werden.

II. Die Brustorgane, speciell das Herz, sind beim ausgesprochenen Enteroptotiker nie in streng normaler Lage.

III. Als klinisch-mathematischer Index der Enteroptose wird der substernale Winkel oder besser der infra-xiphoide Winkel empfohlen, d. h. der Winkel, der durch zwei Linien gebildet wird, die als Tangenten den Bogen der kurzen Rippen berühren an beiden Seiten des Unterleibs und sich an der Spitze des Xiphoidknorpels durchschneiden.

Wenn der Thorax in ausgesprochener Weise in lateraler Richtung komprimiert ist (Trichterthorax), kann es vorkommen, dass die Spitze des Xiphoids nach innen versenkt ist und nicht palpabel ist. In solchen Fällen zieht man am besten mit dem Blaustift Linien an beiden Rippenkanten des Unterleibes entlang und lässt diese einen Winkel bilden unterhalb des Sternums.

Als Instrument zum Messen dieses Winkels wird ein Zirkel mit Masseinteilung empfohlen. Der Knopf des Zirkels wird auf



die Spitze des Xiphoids gelegt und die beiden Schenkel nach unten dicht an den rechten und linken Rippenkanten angelegt. So kann man leicht die Grösse des infra-xiphoiden Winkels ablesen.

Der infra-xiphoiden Winkel ist für jedes Alter und je nach dem Gewicht und der Statur verschieden.

In den Tabellen ist die Durchschnittsgrösse dieses Winkels für jeden dieser Faktoren angegeben.

### Nachtrag.

Während der Korrektur erfuhr ich, dass der belgische Astronom und Anthropologe Quételet zuerst die Aufmerksamkeit auf das „Plurimum“ gelenkt hat — und auch darauf bestanden hat, dass der „arithmetische Durchschnitt“ weder so genau noch so wertvoll ist, wie das Plurimum“. Er nennt diesen anthropometrischen Wert (Value median).

Es ist das derjenige Wert, welcher in der ganzen Serie von Beobachtungen und Messungen so liegt, dass, ebenso viele über wie unter ihm sind, d. h. die Anzahl der Werte, welche er übertrifft, sind gleich der Anzahl, welche ihn übertreffen.

So muss man zugeben, dass Quételet schon vor Pfitzner auf diese wertvolle Art anthropometrische Messungen zu beurteilen hingewiesen hat. (Anthropométrie, ou mesure des diff. facultés de l'homme — Bruxelles 1870.)

Des weiteren ist hinzuzufügen, dass Dr. Winfield Scott Hall (Professor der Physiologie an der Northwestern University in Chicago), eine praktische mathematische Formel vorgeschlagen hat, um diesen Median value zu bestimmen. (W. S. Hall Journal Americ. Med. Ass. Dec. 21. 1901. Evaluation of Anthropometric data.) Er geht dabei zu Werke in folgender Weise z. B. im Bestimmen des Mittel-Kopfumfangs an 314 Individuen.

Angenommen, es sei  $n$  = die Gesamtzahl der Beobachtungen, z. B. 314.  
Angenommen, es sei  $m$  = die Zahl der Beobachtungen in der Mittelgruppe (=69)

„ „  $l$  = Summe „ „ links von der Mittelgruppe

„ „  $r$  = „ „ „ rechts „ „ „

„ „  $a$  = Minimalwert der Mittelgruppe = (56 cm)

„ „  $d$  = Arithmetische Differenz im Minimalwert der Gruppen  
(also  $d$  = 1 cm in W. S. Halls Gruppen) und

$M$  = stelle vor den Mittelwert, den wir suchen,

dann ist

$$M = a + [d (n \div 2 - 1) \div m]$$

oder besser

$$M = \frac{d \frac{n}{2} - l}{a + m}$$

$$M = 56 + [1 (314 \div 2 - 152) \div 69] = 56\frac{5}{69} = 56,072.$$

Ich entnehme die Zahl 314 Halls eigenem Beispiel an Kopfmessungen, doch ist die Formel bei allen anthropometrischen Messungen anwendbar.





# THE HOSPITAL BULLETIN

Published Monthly in the Interest of the Medical Department of the University of Maryland

PRICE \$1.00 PER YEAR

Contributions invited from the Alumni of the University,  
Business Address, 608 Professional Building, Baltimore, Md.

Entered at the Baltimore Post-office  
as Second Class Matter

Vol. VII

BALTIMORE, MD., APRIL 15, 1911.

No. 2

## A PATHFINDER IN THE ETIOLOGY AND PROPHYLAXIS OF YELLOW FEVER,

HENRY R. CARTER, M.D., LL.D.,

SURGEON UNITED STATES PUBLIC HEALTH AND MARINE  
HOSPITAL SERVICE.

By JOHN C. HEMMETER, M.D., PHIL.D., LL.D.,  
*Professor of Physiology, University of Maryland,*  
and

NATHAN WINSLOW, B.A., M.D.,  
*Associate in Surgery, University of Maryland.*

Goethe once classified the various kinds of nature contemplation in a comprehensive way: (1) The lowest grade is represented by the "*Nutzen suchenden*," the utility-seekers who apply that which nature offers for their utilitarian purposes. (2) The second are the "*Wissbegierigen*," or those simply eager for knowledge—the "curious for nature." (3) The third are the "*Auschauenden*," who seek to avoid imagination as far as possible and reduce everything to intuition (from the Latin "*intueri*," to look on or into). (4) The fourth group are die "*Umfassenden*"; these minds operate in the opposite manner from the "intuitionalist," for they start from preconceived ideas and seek to encompass (*umfassen*) their problem by a seeking of a realization of their own ideas in nature.

This classification is a helpful one in endeavoring to understand great minds like that of H. R. Carter.

The discovery of the transmission of the discovery of yellow fever has been credited, and justly so, to the work of Lazear, Reed and Carroll, the latter a member of the class of 1891 of the Medical Department of the University of Maryland. These men, it is true, carried out the experiments which ultimately led to the detection of the manner of conveyance by which yellow fever is communicated from one individual to

another. No fair-minded man can deny this fact, but one name which is closely linked to this epochal discovery has been singularly overlooked—that of Henry R. Carter, class of 1879. His work was no less important than that of the three above mentioned. Therefore we gladly tender this tribute with the view of placing on permanent record the exact part played by Carter in the investigation of yellow fever.

Dr. Henry R. Carter is a native of Virginia; attended the University of Virginia three years; studied medicine at the University of Maryland, taking the degree of Doctor of Medicine therein in 1879. He entered the United States Marine Hospital Service the same year, in which he has served ever since, mainly in sanitary work, especially in connection with yellow fever. On June 1, 1910, his Alma Mater bestowed on him the degree of Doctor of Laws.

This honorary degree was bestowed for reasons that will be set forth in the following.

The work on which he looks back with most satisfaction is:

I. The establishment in quarantine practice of the correct relation between the disinfection (fumigation) of vessels and the detention of their personnel for yellow fever.

In the Regulations of the United States Gulf Quarantine Station of 1888, formulated by him, the detention of the personnel of the vessel, to cover the period of incubation of yellow fever, was first dated from the completion of the disinfection (fumigation by sulphur) of the vessel, their last chance of exposure and infection.

At that time the ports of the United States which required fumigation of vessels for yellow fever dated the period of detention "— days from date of arrival in quarantine," or "from date of departure from last infected port," the number of days varying from "three" to "forty" or "to after frost." But in no case did this period bear any relation to the date of freeing the vessel from infection. It not infrequently happened, then,





HENRY R. CARTER, M.D.

that a vessel would lie her full time—say 20 days—in quarantine and be freed from infection (fumigated) only the day of leaving. Some members of the crew exposed to infection just preceding or during this process in the hold or other seldom-visited parts of the ship would contract yellow fever and develop it after the vessel had docked and they had gone ashore, the period of incubation—five or six days—from the time the fever was contracted being sufficient to allow of this.

This principle is entirely obvious and is the pivot of the whole system of combined disinfection and detention, yet it was ignored not only by United States ports, but in all the British ports considered infectable by yellow fever—Gibraltar, Malta, Jamaica, Trinidad, *et al.*—as well as the French and Danish West Indies, and it was not until the United States Quarantine Regulations became mandatory that it became universal in the United States.

II. Devising a system of maritime quarantine by which such sanitary measures, prevention of infection or disinfection, are taken for vessels in a foreign infected port as will enable them to sail free from infection for the United States from such ports, these measures being rendered possible by corresponding privileges granted at the port of entry to the vessels which adopt them.

This was begun in principle in 1890 and applied extensively in 1893 at the cholera-infected ports of Europe. It is now an integral part of Maritime Quarantine System of the United States, and has been of great value both as a purely sanitary measure and as removing restrictions to commerce, especially the last.

III. Work on the epidemiology of yellow fever, including the determination of its period of incubation in man, and especially the discovery of the "extrinsic incubation" of that disease.

Dr. Henry R. Carter showed that while the existence of a case of yellow fever in an infectable environment can render that environment infectable in a very short time, a few hours, yet a considerable period of time must elapse before that environment becomes infective—that is, capable of communicating yellow fever to other men. This Dr. Carter called the "extrinsic incubation of yellow fever," and fixed its period at "somewhat over 10 days as a minimum." This is in close analogy with the time as determined by Celli and others that elapses between the date of

an anopheles mosquito becoming infected with the parasite of malaria and becoming capable of conveying that disease. This fact was used with much advantage in epidemiological work in 1898 and 1899. The genius of Reed, James Carroll and Lazear (it was Lazear who first spoke to Dr. Carter of its implying a living host) used this thesis as a clue to the problem of the conveyance of yellow fever. It is this that gives it its especial importance, and it is no small gratification to Dr. Carter to think that his work assisted in the epoch-making discovery of Carroll and Reed.

IV. In addition to the above permanent work of enduring excellence, presumably we should call attention to Dr. Carter's work in the yellow-fever epidemics of 1893, 1897, 1898 and 1899, the details of which are on record in the United States Public Health and Marine Hospital Service. In these epidemics he represented the United States; in Louisiana only in 1897; in the entire infected area in 1898 and 1899. This was purely executive work, and was done with practically no authority, "in co-operation with State and local health authorities." Yet it was adjudged to have been successful. In his districts commerce was carried on fairly well, panic was quieted, and there was no spread of fever to new sections. In 1898, working with the Mississippi health authorities, the epidemic of yellow fever at McHenry, a town in Southern Mississippi, was suppressed. This was the first instance of an epidemic of yellow fever in the far South, well under way, in June and July, being suppressed.

The method used was the control of the human host. The conveyance by the stegomyia was *not* then known, and, except the unnecessary disinfection of clothing, was not all adapted to that end, even in the modern light of the mosquito conveyance. The same methods here instituted were used successfully by White and Von Ezdorf in an outbreak of yellow fever at Hampton, Va., two years later.

We have contrasted this executive work with permanent original or research work. This class of executive work bears the same relation to, say, the determination of the extrinsic incubation of yellow fever that a campaign, the troops using firearms, does to the discovery of gunpowder. The strategist avails himself of what the investigator discovers.

As an estimate of the value of Dr. Carter's work the following letters are appended:

Board of Health Laboratory,  
Ancon, Canal Zone, October 4, 1909.  
Dr. William Royal Stokes,  
City Hall Annex,  
Baltimore, Md.

Dear Dr. Stokes:

Before I forget it again I must write to you about a matter that has been on my mind for several months. Dr. H. R. Carter, who was our first Chief Quarantine Officer, and for four and one-half years Director of Hospitals here, has returned to the States, to be located at Louisville, Ky.

Dr. Carter, as you know, by his wonderfully keen observations made during several epidemics of yellow fever, particularly the one in Louisiana, brought out his theory of an "extrinsic period of incubation," which was of the greatest value in helping Reed to a successful issue in his yellow-fever experiments.

Ronald Ross told me in Liverpool three years ago that he had put in Dr. Carter's name for the Nobel prize. Dr. Carter has never received quite the recognition he deserves for his yellow-fever observations and for his pioneer quarantine work.

As you and he are alumni of the University of Maryland, I want to suggest that you use your influence in getting an honorary degree from the University for him next year. I cannot see why he has been neglected, for his work is recognized abroad and in all literature on the subject, and his name will always be linked with Finlay's in connection with yellow fever.

Reed in letters to Dr. Carter told him how valuable Dr. Carter's observations had been to him in his yellow-fever work.

I sent some slides showing malarial zygotes and sporozotes to Dr. Pearce of Winnipeg, and hope they were of some value to him.

With kindest regards to Mrs. Stokes and the children, I am,

Yours very truly,  
S. T. DARLING.

I have also made the suggestion to Dr. Perry, our present quarantine officer, about the honorary degree for Dr. Carter.

Board of Health Laboratory,  
Ancon, Canal Zone, December 1, 1909.  
Dr. William Royal Stokes,  
City Hall Annex,  
Baltimore, Md.

Dear Dr. Stokes:

I have received from the members of Dr. Carter's family data relating to his work, investigations and published researches in compliance with your request of October 14.

1st. *The determination of the period of incubation of yellow fever:*

The determination of the period of incubation

of yellow fever in man and the placing of the period of quarantine detention of the personnel for this disease on a rational basis, dating it from their last exposure. The completion of disinfection to cover the period of incubation, while all ports of the United States and Great Britain were dating it from the hour of arrival in quarantine to leaving the infected port, the period of this detention being apparently chosen arbitrarily, as no two ports had the same. The disinfection of vessels on leaving ports infected with yellow fever and dating the time of detention from this disinfection so that the days *en route* would count as days in quarantine. This, of course, he applied to all vessels leaving ports where quarantinable diseases carried by vessels prevailed.

2d. *The discovery that there was a period of "Extrinsic Incubation" in its environment for yellow fever and the approximate determination of its minimum duration as somewhat over 10 days:*

By "extrinsic incubation" was meant that a certain considerable period of time must elapse between the date that a place received infection from a yellow-fever patient before it became infective, *i. e.*, capable of conveying it to other men. These investigations were begun in 1888. The article was written in December, 1899, and January, 1900, and published in May, 1900. He himself, however, had been using it as a working basis for several years before—no one else accepting it.

3d. *Quarantine work at Chandeleur and Ship Island in 1888 to 1892:*

What was really done at Ship Island and Chandeleur was the establishment of the United States Maritime Quarantine System and the systematization of the quarantine methods for yellow fever. Prior to this time the State quarantine stations of the South Atlantic and Gulf ports differed among themselves in regulations, methods of disinfection and period of incubation, and no one station was willing to take the pratique of the other. His effort at Ship Island was to get them all to agree upon one method of handling vessels, doing all that was necessary and nothing that was believed to be unnecessary. That was successful, and before he left the Southern ports accepted the pratique of the United States stations.

It was while here that he formulated his ideas of disinfecting vessels at the port of departure so that the days *en route* should count as days in quarantine. This was proposed at the meeting of the American Public Health Association at Charleston, S. C., in 1890. It was regarded as impracticable by some and dangerous by others, but is now universally accepted by sanitarians and is the key to practically all the methods of the United States quarantine. Its benefits to commerce can readily be imagined. It was also here, while working upon the problem of the incubation of yellow fever in man, that he discovered the phenomenon of the "extrinsic incubation" of that disease in infected places, which he subsequently



worked out in 1898. Prior to this time, however, he was sufficiently convinced of its truth to use it as a working basis.

Since leaving Ship Island and Chandeleur he has held every quarantine station of the United States from Ship Island to Delaware Breakwater, and had much to do with founding and equipping them. He had charge of the train inspection, communication and everything save measures in the city in the Brunswick epidemic of yellow fever in 1893. He was in charge of the measures in Louisiana and the train inspection in the epidemic of 1897. He was in charge of the South in the epidemics of 1898 and 1899. In 1898 he was in charge of the epidemic of yellow fever in the little town of McHenry, Miss., which was, it is believed, the first place in the South in which an epidemic of yellow fever had ever been stamped out in the summer time. He organized and had charge of the quarantine of the Island of Cuba in 1899-1900.

#### SOME OF HIS PUBLISHED RESEARCHES.

1st. "A Note on the Interval Between Infecting and Secondary Cases of Yellow Fever from the Records of Yellow Fever at Orwood and Taylor, Miss., 1898."—*The New Orleans Medical and Surgical Journal*, May, 1900.

2d. "A Note on the Spread of Yellow Fever in Houses—the 'Extrinsic Incubation.'"—*Medical Record*, June 15, 1901.

This was written for the medical convention that met at Havana February, 1901.

3d. "A Correlation of Some Facts in the propagation of Yellow Fever, with the Theory of Its Conveyance by the *Culex fasciatus*."—*Philadelphia Medical Journal*, April 6, 1901.

This was written while he was sick in hospital in Baltimore in November, 1900.

4th. "Are Vessels Infected with Yellow Fever? Some Personal Observations."—*Medical Record*, March 22, 1902.

5th. "Some Characteristics of the *Stegomyia fasciatus* which Affect Its Conveyance of Yellow Fever."—*Medical Record*, May 14, 1904.

6th. "The Conveyance of Yellow Fever."—*Medical News*, November 5, 1904.

Read before the Texas State Medical Association April 27, 1904.

7th. A little memorandum written April 6, 1906: published in the *Medical Record*—date not known—aiming to show that yellow fever was habitually contracted in the daytime, at least in Panama, in contravention of the statement of Marchaux, Simon and Salimbini.

Besides this, there have been a number of articles written for publication by the service, giving in detail the measures necessary in handling yellow-fever epidemics—i. e., train inspection, communications with a town infected with yellow fever, etc. There have been, also, articles on other professional subjects, the first one in 1882, entitled "Syphilis in the Negro."

#### RECENT PAPERS.

"Recent Advances in Tropical Medicine." Read before the Pan-American Scientific Congress held at Santiago, Chili, December 25, 1908, to January 5, 1909.

"Malarial Fever Work on the Isthmus." Read before the Canal Zone Medical Association in 1908.

In 1905 or 1906 Dr. Carter's name was presented for the Nobel prize in medicine. At that time he prepared a statement of his relations to the study of yellow fever as a sanitarian and an epidemiologist. The substance of Dr. Carter's statement is outlined above. There is no doubt that Dr. Carter's researches induced Durham and Walter Meyer to make the yellow-fever investigation at Pará, and that it actually influenced (and as to time determined) the direction of Reed's investigations as well is borne out by many verbal and written statements by him. Dr. Reed had been much impressed by the valuable observations made at Orwood and Taylor, Miss., by Dr. Carter on the interval between infecting and secondary cases of yellow fever. Experiments by Dr. Reed confirmed those already mentioned by Dr. Carter in 1898 that at least 12 days must elapse between contamination of the mosquito by the blood of a yellow-fever patient and the communication of the disease. Ronald Ross regarded Dr. Carter's observations on the extrinsic period of incubation of yellow fever as an extremely important one in its relation to the work of the Yellow Fever Commission in Cuba. Dr. Ross has recently invited Dr. Carter to contribute a chapter on his forthcoming book on tropical hygiene.

The above memoranda expresses in bare outlines Dr. Carter's work in connection with yellow fever, sanitation and quarantine.

Very truly yours,

S. T. DARLING.

Baltimore, Md.

Dr. John C. Hemmeter:

Dear Doctor—A number of the friends of Dr. H. R. Carter have thought for some time that it would be a deserving honor for him if his Alma Mater, the University of Maryland, could confer an honorary degree upon him on account of the early and important work which he carried out and which led directly to the brilliant discoveries of Reed and of his assistants concerning the transmission of yellow fever by the mosquito. I am informed by Dr. S. T. Darling, who has charge of the hygienic laboratory of the Canal Zone, that Dr. Carter has left the Isthmus and is about to settle in Louisville. Dr. Darling has very carefully collected the data which we enclose, and I think that you will agree that this work is deserving of proper recognition. On the other hand, it adds to the glory of our Alma Mater to emphasize such humanitarian work when performed by one of her sons. We therefore respectfully ex-



press the wish and hope that you will attempt to secure an honorary degree for Dr. Carter.

The following is the data collected by Dr. Darling concerning the work, investigations and published researches in compliance with your request of October 14:

1st. *The determination of the period of incubation of yellow fever:*

The determination of the period of incubation of yellow fever in man and the placing of the period of quarantine detention of the personnel for this disease on a rational basis, dating it from their last exposure. The completion of disinfection to cover the period of incubation, while all ports of the United States and Great Britain were dating it from the hour of arrival in quarantine to leaving the infected port, the period of this detention being apparently chosen arbitrarily, as no two ports have the same. The disinfection of vessels on leaving ports infected with yellow fever and dating the time of detention from this disinfection so that the days *en route* would count as days in quarantine. This, of course, he applied to all vessels leaving ports where quarantinable diseases carried by vessels prevailed.

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By "extrinsic incubation" was meant that a certain considerable period of time must elapse between the date that a place received infection from a yellow-fever patient before it became infective, *i. e.*, capable of conveying it to other men. These investigations were begun in 1888. The article was written in December, 1899, and January, 1900, and published in May, 1900. He himself, however, has been using it as a working basis for several years before—no one else accepting it.

3d. *Quarantine work at Chandeleur and Ship Island in 1888 to 1892:*

What was really done at Ship Island and Chandeleur was the establishment of the United States Maritime Quarantine System and the systematization of the quarantine methods for yellow fever. Prior to this time the State quarantine stations of the South Atlantic and Gulf ports differed among themselves in regulations, methods of disinfection and period of incubation, and no one station was willing to take the pratique of the other. His effort at Ship Island was to get them all to agree upon one method of handling vessels, doing all that was necessary and nothing that was believed to be unnecessary. That was successful, and before he left the Southern ports accepted the pratique of the United States stations.

It was while here that he formulated his idea of disinfecting vessels at the port of departure so that the days *en route* should count as days in quarantine. This was proposed at the meeting of the American Public Health Association at Charleston, S. C., in 1890. It was regarded as

impracticable by some and as dangerous by others, but is now universally accepted by sanitarians and is the key to practically all the methods of the United States Quarantine. Its benefits to commerce can readily be imagined. It was also here, while working upon the problem of the incubation of yellow fever in man, that he discovered the phenomenon of the "extrinsic incubation" of that disease in infected places, which he subsequently worked out in 1898. Prior to this time, however, he was sufficiently convinced of its truth to use as a working basis. Since leaving Ship Island and Chandeleur he has held every quarantine station of the United States from Ship Island to Delaware Breakwater, and had much to do with founding and equipping them. He had charge of the train inspection, communication and everything save measures in the city in the Brunswick epidemic of yellow fever in 1893. He was in charge of measures in Louisiana and the train inspection in the epidemic in 1897. He was in charge of the South in the epidemics of 1898 and 1899. In 1898 he was in charge of the epidemic of yellow fever in the little town of McHenry, Miss., which was, it is believed, the first place in the South in which an epidemic of yellow fever had ever been stamped out in the summer time. He organized and had charge of the quarantine of the Island of Cuba in 1899-1900.

#### SOME OF HIS PUBLISHED RESEARCHES.

1st. "A Note on the Interval Between Infecting and Secondary Cases of Yellow Fever from the Records of Yellow Fever at Orwood and Taylor, Miss., 1898."—*The New Orleans Medical and Surgical Journal*, May, 1900.

2d. "A Note on the Spread of Yellow Fever in Houses—the 'Extrinsic Incubation.'"—*Medical Record*, June 15, 1901.

This was written for the Medical convention that met at Havana February, 1901.

3d. "A Correlation of Some Facts in the Propagation of Yellow Fever, with the Theory of Its Conveyance by the *Culex fasciatus*."—*Philadelphia Medical Journal*, April 6, 1901.

This was written while he was sick in hospital in Baltimore November, 1900.

4th. "Are Vessels Infected with Yellow Fever? Some Personal Observations."—*Medical Record*, March 22, 1902.

5th. "Some Characteristics of the *Stegomyia fasciatus* which Effect Its Conveyance of Yellow Fever."—*Medical Record*, May 14, 1904.

6th. "Conveyance of Yellow Fever."—*Medical News*, November 5, 1904.

Read before the Texas State Medical Association April 27, 1904.

7th. A little memorandum written April 6, 1906; published in the *Medical Record*, date not known, aiming to show that yellow fever was habitually contracted in the daytime, at least in Panama, in contravention of the statement of Marchaux, Simon and Salimbini.

Besides this, there have been a number of articles written for publication by the service, giving in detail the measures necessary in handling yellow-fever epidemics—*i. e.*, train inspection, communications with a town infected with yellow fever, etc. There have been, also, articles on other professional subjects, the first one in 1882, entitled "Syphilis in the Negro."

#### RECENT PAPERS.

"Recent Advances in Tropical Medicine." Read before the Pan-American Scientific Congress, held at Santiago, Chili, December 25, 1908, to January 5, 1909.

"Malarial Fever Work on the Isthmus." Read before the Canal Zone Medical Association, 1908.

In 1905 or 1906 Dr. Carter's name was presented for the Nobel prize in medicine. At that time he prepared a statement of his relations to the study of yellow fever as a sanitarian and epidemiologist. The substance of Dr. Carter's statement is outlined above. There is no doubt that Dr. Carter's researches induced Durham and Walter Meyer to make the yellow-fever investigation at Pára, and that it actually influenced (and as to time determined) the direction of Reed's investigations, as will be borne out by many verbal and written statements by him. Dr. Reed had been impressed by the valuable observations made at Orwood and Taylor, Miss., by Dr. Carter on the interval between infecting and secondary cases of yellow fever. Experiments by Dr. Reed confirmed those already mentioned by Dr. Carter in 1898 that at least 12 days must elapse between the contamination of the mosquito by the blood of the yellow-fever patient and the communication of the disease. Ronald Ross regarded Dr. Carter's observation on the extrinsic period of incubation of yellow fever as an extremely important one in its relation to the work of the Yellow Fever Commission in Cuba. Dr. Ross has recently invited Dr. Carter to contribute a chapter on his forthcoming book on tropical hygiene.

The above memoranda expresses in bare outlines Dr. Carter's work in connection with yellow fever, sanitation and quarantine.

Yours very truly,

WILLIAM ROYAL STOKES.

#### CONCLUSION.

We have now reached a sufficient degree of familiarity with Carter's work and the method of his research and thinking to recognize that he belongs to Goethe's "*Auschauenden*." He is clearly an objective worker who seeks to avoid imagination as far as possible, and humbly submits to the hard facts of observation and experiment.

The day will come when some great thinker—a medical Bancroft—will write the history of American medicine, and then such pioneers and

heroes as James Carroll and Henry R. Carter will stand out on the roll of honor in the American Medical "*Walhalla*" as brilliant as the names of any scientists, artists, statesmen, naval or military heroes our nation has ever produced. And this is to let the world know that they are sons of the University of Maryland.

#### A CASE OF PERSISTENT VOMITING FOLLOWING GASTRO-ENTEROSTOMY, PERFORMED FIVE YEARS AGO—SECOND ABDOMINAL SECTION, DECEMBER, 1910—CHEMIC AND PHYSIOLOGIC STUDY OF DISTURBED COORDINATION BETWEEN THE STOMACH AND DUODENUM.

*Reported and shown by*

ALBERT H. CARROLL, M.D.; E. E. NICHOLS, *Senior Medical Student*, and W. C. MARETT, *Senior Medical Student in Prof. John C. Hemmelter's Clinic on Diseases of Digestion and Metabolism, University of Maryland.*

This interesting case which we have to present today is one of those obstinate cases of vomiting, with quantities of bile in the vomita, with emaciation, anemia and with marked nervous symptoms. An atrophic pancreatic condition was at first suspected and carefully looked for. The findings were negative.

We are now convinced that this is a case of what is commonly called "vicious circle," following a gastro-enterostomy. This operation was done five years ago. It appears to us that relief will only be had by undoing the work then done, and this has been recommended.

Entrance note. History.

Name, C. E.; age, 30 years; occupation, fireman on steamship of Hamburg-American line; social condition, single.

The patient entered this hospital December 5, 1910, complaining of stomach trouble. He first had trouble with his stomach eight years ago, when he had severe fullness and "hardness" after eating, with frequent vomiting. He was treated for two years; his stomach was washed out every night. Six years ago—two years after his trouble began—he was operated on in Hamburg, Germany, by Professor Urban. At that time a gastro-enterostomy was done. Fourteen days ago he noticed a sensation of burning and heaviness in the



epigastric region, coming on about one hour after taking food. This was relieved either by vomiting (which was frequent) or disappeared in about two hours. For the first six or seven days he kept on working, but since then he has been confined to bed.

The vomitus is "lime-green" in color. Before this operation was performed the patient "vomited blood" twice. His appetite is poor; the bowels are regular. The first six days' stools were black and tar-like. No history of jaundice.

Examination for occult blood was not made till later, and was not found then.

*Habits.*—Patient worked five years in a brewery in Germany, during which time he drank beer in large quantities. A history of other dietary indiscretions or of trauma at any time was not obtained. We must remember that he is a stoker.

*Family History.*—Father died in 1880 in Australia. Mother living and well; one sister and one brother living and well. Negative to cancer, tuberculosis, gout, epilepsy, etc.

*Past History.*—Negative to diphtheria, tuberculosis, measles, scarlet fever, rheumatism, pneumonia and pleurisy. Had typhoid lasting six weeks while in Argentina, S. A., two years ago. He had an attack of gonorrhea at the age of 20 years which lasted nine months, and again at 28 years of age, which lasted five weeks. Past history otherwise negative, except such troubles as above described.

*Present Illness.*—While at work about two weeks ago he was taken with pains of a dragging, dull character in his epigastrium, followed by sour eructations of a burning character and by vomiting. He says that the vomitus was largely composed of mucus of a whitish-gray color. Since then he has had numerous cramps—like attacks which were followed by the vomiting of a greenish substance. Owing to poor digestion and assimilation, he is weak and has lost weight. He is very downcast and discouraged.

*Physical Examination.*—The patient is a fairly well-developed white man, with muscles of fair tone. The head is round, and is covered with a good crop of light hair. Forehead receding; no scars. Ears, no topi, mastoid tenderness or discharge. Nose, no discharge or tenderness over accessory sinuses. Eyes, pupils equal and react to light and accommodation, conjunctiva somewhat injected, sclera clear, ocular movement good. Mouth, teeth in bad state of preservation, pyor-

rhea marked. Tongue protrudes in the median line, slight tremor. Dorsum fairly clear, breath foul. No tonsillar enlargement. Neck well developed, post-cervical glands palpable. No abnormal pulsations or tracheal tug. Thyroid gland not palpable.

*Chest.*—Fairly well developed, palpation and percussion normal and equal. Auscultation, voice sounds are decreased on the left side.

*Heart.*—P. M. I. neither visible nor palpable. Sounds at apex beat heard at fifth interspace, to the inner side of M. C. L., of good tone and quality. No murmurs were heard; absolute cardiac dullness is not increased.

*Abdomen.*—Liver dullness begins at seventh rib, and palpable two fingers' breadth below costal margin. A median post-operative scar is noted above the umbilicus; it is about three inches in length.

*Stomach.*—Extends to the umbilicus, and gurgling sounds were heard on direct percussion, otherwise negative. Inguinal glands palpable.

*Genitalia.*—Large, bilateral varicocele. No scar.

*Extremities.*—Poorly developed. His reflexes are normal. The axillary and epitrochlear glands are palpable. Pulse regular, tension and volume fair, and rhythm good.

This case was referred from the medical to the surgical side, and an exploratory laparotomy advised. The abdomen was opened by Dr. J. Holmes Smith, and it was found that a gastro-enterostomy had been performed. The stomach was opened, and both the pyloric and the artificial opening found patent. No evidence of a past or present ulcer was present, or at least not observed. A large intestinal loop had been used. No obstruction was found, and the openings in the stomach and in the abdomen were closed in the usual way.

The patient's condition at first led us to suspect an atrophic pancreatitis. (Later findings negate this diagnosis.)

It has been noted that gastro-enterostomies are frequently followed by an atrophy of the pancreas. (The normal stimulation of the pancreas is due in part to the action of the acid gastric contents on the papilla of Vater. This is supposed to send a reflex stimulation to the pancreas and excite it to action.)

There are but few physical symptoms or signs by which a positive diagnosis of atrophy of the pancreas can be made. The pancreas is not normally a palpable organ. Small cubes of boiled

Archiv  
für  
**Verdauungs-Krankheiten**

mit Einschluss der  
**Stoffwechselfathologie und der Diätetik**

herausgegeben von

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redigiert von

**PROFESSOR DR. I. BOAS**

in Berlin.

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**Sonder-Abdruck aus Band XVII. Heft 2. (1911.)**

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(Aus dem physiologischen Laboratorium der Universität von Maryland.)

**Zur Geschichte der Duodenal-Intubation und der  
physiologischen Chemie des menschlichen Pankreas.**

Von

**JOHN C. HEMMETER,**

Professor der Physiologie und Direktor des Physiologischen Laboratoriums der Universität  
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**BERLIN**  
**VERLAG VON S. KARGER**  
KARLSTRASSE 15.

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Die palpablen Gebilde des normalen menschlichen Körpers  
und deren

**Methodische Palpation.**

Nach eigenen Untersuchungen an der Leiche und am Lebenden

Von

**Dr. Toby Cohn**

Nervenarzt in Berlin.

**I. Teil: Obere Extremität.**

Mit 21 Abbildungen im Text. Brosch. M. 5,60.

**Zeitschr. f. phys. u. diätet. Therapie:** . . . verdienstvolle Buch, das aufs dankbarste von jedem Arzte begrüßt werden wird, dem Genauigkeit der Untersuchung am Herzen liegt. Mit Spannung sehen wir der Fortsetzung des Werkes entgegen, das wir heute schon nicht mehr entbehren zu können glauben.

**Deutsche Medizinalztg.:** . . . In der Tat, ein originelles Werk. In erschöpfender Weise, ohne aber jemals langweilig zu werden, weiss Verfasser seinem Gegenstande stets neue praktische Seiten abzugewinnen, so dass jeder Arzt und Kliniker hier vielerlei Neues und vielerlei Anregung für Diagnosen- und wohl auch Prognosenstellung gewinnen wird. Es ist dieses Werk geradezu ein Ereignis auf dem ärztlichen Büchermarkt, und wir sehen mit Spannung den folgenden Bänden entgegen.

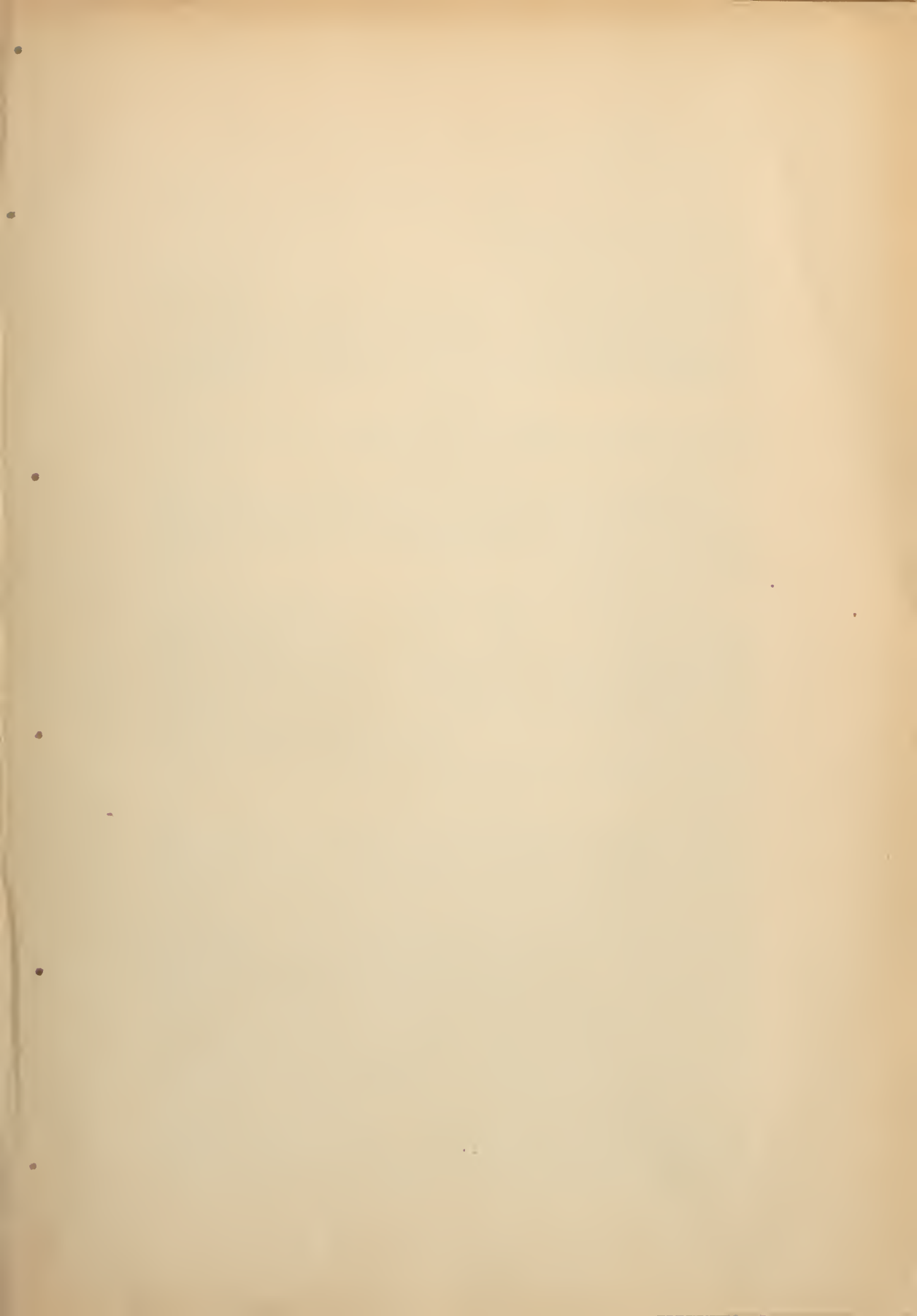
**Deutsche med. Wochenschr.:** Es ist verwunderlich, dass ein solches Buch nicht schon lange geschrieben ist, eine topographische Anatomie aller dem tastenden Finger irgendwie zugänglichen Gebilde, die dem Internisten und Chirurgen, dem Neurologen und dem wissenschaftlichen Masseur ein gleich willkommenes und unentbehrliches Hilfsmittel sein wird. So gut wie alles, was der Verfasser uns bietet, beruht auf eigener Untersuchung und Beobachtung. Die physiologischen Variationen sind ausführlich berücksichtigt, auch das anthropologische Material ist in erheblichem Umfange herangezogen. Die Darstellung ist geschickt, oft merkt man kaum, dass man doch eigentlich einen ziemlich trockenen Stoff vor sich hat: das Gebiet ist wohl völlig erschöpft. Hoffen wir, dass die folgenden Teile nicht zu lange auf sich warten lassen.

**II. Teil: Untere Extremität.**

Mit 39 Abbildungen im Text und auf 9 Tafeln. — Preis M. 6,40.

**Deutsche Zeitschrift für Chirurgie, Band 97:** Man kann es nur bedauern, dass dem überall günstig aufgenommenen I. Teil dieses Buches die Fortsetzung erst so spät gefolgt ist. In einer Zeit, die bei der hohen Ausbildung anderer Untersuchungsmethoden dazu angetan ist, die methodische Palpation des normalen menschlichen Körpers weniger wichtig erscheinen zu lassen, ist ein solches Buch besonders lebhaft zu begrüßen. Mag der Stoff an sich auch etwas spröde sein, dem Verfasser ist es trefflich gelungen, durch fesselnde Darstellung, durch Einstreuen anthropologischer Bemerkungen, durch Berücksichtigung physiologischer Variationen jede Ermüdung des Lesers zu vermeiden. Speziell dem Lehrer, der in der Klinik oder in Kursen die Studierenden nicht oft genug auf die dem Auge und der palpierenden Hand zugänglichen Gebilde des menschlichen Körpers aufmerksam machen kann, ist dieses Buch von neuem warm zu empfehlen. Wie der Chirurg, so wird der Internist, der Neurologe Nutzen aus ihm ziehen können. Der II. Teil enthält auf 160 Seiten die Schilderung der palpablen Gebilde der Gesäß- und Leistengegend bis herab zum Dorsum und der Planta pedis und den Zehen.

**Archiv f. klin. Medizin:** . . . Der zweite etwas umfangreichere Teil steht vollkommen auf der Höhe des ersten, so dass die Erwartungen, die man nach Erscheinen des ersten Teiles an die Fortsetzung des Werkes knüpfte, vollauf erfüllt wurden. Das reich und ganz vorzüglich illustrierte Buch dürfte neben seinem Wert als Lehrbuch für die verschiedensten Gebiete der Praxis, besonders auch für die Unfall-Untersuchung ein unentbehrlicher, vielbegehrter Führer sein.



(Aus dem physiologischen Laboratorium der Universität von Maryland.)

## **Zur Geschichte der Duodenal-Intubation und der physiologischen Chemie des menschlichen Pankreas.**

Von

**JOHN C. HEMMETER,**

Professor der Physiologie und Direktor des Physiologischen Laboratoriums der Universität  
von Maryland.

In letzterer Zeit sind vier Veröffentlichungen über obiges Thema erschienen, in welchen wahrscheinlich in unbeabsichtiger Weise frühere Arbeiten auf demselben Gebiete nicht die gebührende Anerkennung finden.

Die Intubation des Duodenum vom Munde aus ist schon vor zwölf Jahren eine bedeutend entwickelte Methodik gewesen. Soweit die Überwindung des rein experimentellen Stadiums dieser Bemühungen bei einem so komplizierten Objekt wie es der menschliche Verdauungstraktus darstellt, möglich war, ist auch die Intubation des menschlichen Duodenums durch *F. Kuhns* Arbeiten in dieser Beziehung gelungen. Aber auch physiologische wie pathologische Befunde hat diese Methode schon vor zwölf Jahren geliefert.

Nun kommt die Frage, warum wird diese Methode nicht häufiger gebraucht, und warum hat sie seit meinen ersten Versuchen nicht mehr geleistet, bis sie kürzlich wieder neu entdeckt worden ist. Ich gebe zu, in verschiedener Form von *F. Kuhns* und meiner Technik. Die Antwort wird verschieden lauten, je nachdem die Fragestellung pathologische oder physiologische Ziele verfolgt. Zur Erforschung pathologischer Zustände ist der Mensch ein gerechtfertigtes Objekt. Die Intubation geschieht zum Zwecke eines besseren Verständnisses seines krankhaften Zustandes; dient eventuell zur Heilung. Aber zur physiologischen Erforschung angewandt, wird der Mensch zum Versuchsobjekt.

Nun wird die Methode selten Anwendung finden, erstens, weil pathologische Zustände, die eine solche Methode erheischen, im Grunde genommen selten sind, zum Teil durch einfachere Prozeduren in speziellen Fällen ersetzt werden können. Es kommt

darauf an, was man herausfinden will, ob veränderte Peristaltik, Stenose oder krankhafte Sekretion etc.

Für die physiologische Untersuchung selbst des menschlichen Duodenums und Pankreas bietet die Chirurgie bessere Gelegenheit, wie wir gleich erkennen werden, und das Tierexperiment ist für diese Zwecke entschieden das genauere. Alle Versuche, am menschlichen Pankreas oder Duodenalsaft etwas vom Tierexperiment gefundenes zu verbessern oder neues hinzuzufügen, sind nicht erfolgreich gewesen, also neue Beiträge zur Physiologie des Pankreas liefert das Experiment am Menschen *nicht*.

Wie *Glaessner* schon vor sechs Jahren berichtet („Über menschliches Pankreassekret“ *Hoppe Seylers Zeitschr. für physiol. Chem.* 1903. Bd. 40, S. 465) waren damals schon eine Reihe von Untersuchungen bekannt, die den menschlichen Bauchspeichel betreffen. Dieses Sekret war jedoch bis zu *Glaessners* Bericht in mehr oder weniger pathologischer Form Gegenstand der Forschung gewesen.

Die Resultate von *Schumm* jedoch („Über menschliches Pankreassekret *Hoppe Seylers Zeitschr. f. physiol. Chem.* Bd. 36. S. 298) stimmen im Allgemeinen mit den erlangten physiologischen Tatsachen überein. Auch meine Befunde am Duodenum des Menschen (*Diseases of the Intestines*, Vol. I. p. 266—280) waren physiologische Ergebnisse.

In den *Internationalen Beiträgen zur Pathologie und Therapie der Ernährungsstörungen*. Bd. II. Zweites Heft. S. 184, unter dem Titel „*Studien über den Duodenalinhalt des Menschen*“, veröffentlichten Dr. *Max Einhorn* und *Jacob Roosenblom* eine Methode und eine Arbeit in Worten, die von allen schon publizierten Untersuchungen und Methoden auf demselben Gebiete nichts erwähnen, obschon *Franz Kuhn* (*Arch. f. Verdauungskrankheiten* Bd. III. S. 19, 1898) in technisch vollendeter Weise dasselbe Ziel der Duodenalintubation vollkommen erreicht hat und selber anerkennt, dass ich ihm sogar vorausgegangen bin, was durch meine Veröffentlichung in *Boas Archiv f. Verdauungskr.*, Bd. II, S. 98, im Jahre 1896 — bewiesen wird. (*Hemmeter*, „*Versuche über Intubation des Duodenum*“ l. c. Bd. II, S. 98.)

*Kuhn* hat nun die Methodik der Intubation des Verdauungstraktus von verschiedenen Richtungen her tatsächlich zu einer exakten Kunst entwickelt. (Siehe *F. Kuhn*, „*Metallschlauchsonde*“, l. c. III, 106, „*Metallspiralsonden*“, l. c. IV, 85, „*Dick-*



darmsondierung“, l. c. IV, 486, „Sondierung des Pylorus“, l. c. III, 107 u. 339, „Mastdarmrohr“, l. c. IV, 208.

Vor zwölf Jahren hat Herr Kollege *Kuhn* mein Institut in Baltimore mit seinem Besuche beehrt, bei welcher Gelegenheit ich von der Überlegenheit seiner Methode über die meinige so überzeugt wurde, dass ich seither nur *Kuhns* Instrumente zur Duodenalintubation gebrauchte.

Niemals stand es mir im Sinn, dass meine vor 15 Jahren erfundene Methode der Duodenalintubation die einzige bleiben würde, denn ich sagte damals (Arch. f. Verdauungskr. Bd. II, S. 85, 1896) ausdrücklich, dass ich „*nur die Anfangsgründe für zukünftige Arbeiten in diesem Felde niederlegen wollte und die Richtung angeben, in welcher nach und nach eine sichere Manipulation zu erhoffen ist.*“

Des weiteren sagte ich (l. c.): „Ich veröffentliche diese Methode mit der Schüchternheit, die ein gerechtes Misstrauen in ihre praktische Verwertbarkeit mir einflößen muss.“

Nun hat sich diese erste Methode dennoch bewährt, denn in meinem Laboratorium wurden interessante Tatsachen über das menschliche Pankreas festgestellt, die in meinem Handbuch über Darmkrankheiten veröffentlicht sind (*Hemmeter*, „*Diseases of the Intestines*“, Vol. I., p. 263 to 272).

In demselben Bande gebe ich dem *Kuhnschen* Instrument den Vorzug („*Kuhns method is more practical than my own, because the instrumentes are simpler in construction. S. 267 etc. and permit of entrance into the Duodenum with greater surety,*“ etc.). Der geschichtlichen Rechtfertigung wegen zitiere ich die Angaben in meinem englischen Werke (l. c. 267), die sich auf einige meiner physiologischen und pathologischen Befunde während dieser Studien beziehen.

In May, 1897, I had under observation a female patient who had suffered repeated biliary colic. At times she passed small stones without giving her much pain, at least they were found in the stools without having given her any colic. She was deeply jaundiced and willing to undergo an operation to be relieved. Through the comparatively thin abdominal walls we were able to feel numerous stones in the gall-bladder. She consented to an attempt at intubation of the duodenum to determine whether there was any bile secreted. The duodenum was entered without difficulty, and cleaned by running in and aspirating out distilled warm water. Twelve hours afterward, no food having been taken

in the meanwhile, the duodenum was again intubated according to our method, and washed with 100 c. c. of warm distilled water.

„On being aspirated, the water was still clear, but viscid and sticky, similar to a solution of eggalbumen. It contained no bile-pigments nor cholesterin, and was free from taurocholates and glycocholates. It was colorless and odorless, and seemed very rich in some form of albumin. That it was a solution of pancreatic juice was proved by its digesting fibrin and serum albumin. (In alkaline medium.)“

„The juice obtained in this manner digested from 85 to 95 per cent of Mercks dried serum albumin in the digestorium at 100 F. in two hours. The amylolytic and fat-decomposing property of the juice was determined in a similar manner. One is therefore justified in concluding that in this case the pancreatic juice was obtained almost pure, as there were no bile elements contained in it, the bile being prevented from entering“ the duodenum by a calculus or catarrhal occlusion in the common duct. This is an evidence that these are cases of occlusion or stenosis of the common gall-duct not involving the pancreatic duct. As there are also pancreatic calculi, or occlusions of the duct by neoplasm or catarrhal swelling, it is conceivable that we may yet be able to obtain the bile in a pure condition, and free from pancreatic juice, from the human subject, without operation.“

„In one patient in whom I had intubated the duodenum successfully on five different occasions I had an opportunity of seeing the stomach at an operation undertaken for the relief of pyloric stenosis due to hyperplasia. The stomach was in no way injured; neither have I been able to discover, on the stomachs of dogs, that the sound can produce any injury to the gastric mucosa when it is properly handled — and it should not be handled at all unless it can be properly handled. It should first be learned upon the cadaver and on animals before it is attempted on the living subject. One of the earliest reference to duodenal intubation in American literature was published by Dr. Fenton B. Turck of Chicago, in „Amer. medico-surgical bulletin July 1895, vol. VIII, No. 13, page 772.“

„The amylolytic, proteolytic and adipolytic power of the duodenal chyme was tested by standardized solutions of pure starch, weighed amounts of fibrin, prepared according to the directions of Chittenden („Amer. Jour. of the Med. Sci.“ vol.

III, p. 39), and weighed amounts of pure sterilized olive oil. It was found: (1) That these enzymatic powers of the pancreatic juice as obtained from the duodenal chyme, mixed with bile varied under normal conditions in the same individual; (2) that they varied with different food substances- (3) that fat (olive oil) was a powerful dietetic stimulant to the secretion of pancreatic juice (J. P. Pawlow, „Arbeit der Verdauungsdrüsen“, S. 160); (4) that the digestive activity of the various pancreatic ferments is more energetic when the gastric secretion and peristalsis are normal, than in cases of achylia gastrica, where the secretion of HCl and of the gastric ferments is wanting, the digestive power“ of the pancreatic ferments was decidedly inferior to that from cases with normal gastric digestion. I examined four cases of achylia gastrica particularly for this point, and in all four the duodenal digestion was evidently inferior to that found in individuals with normal stomachs. It seems, therefore, that a normal secretion of pancreatic juice is dependent upon a normal secretion of HCl in the stomach. A disease of the stomach suppressing the secretion of HCl robs the pancreas of one of its chief stimulants to secretion. This is also in accordance with the observations of J. P. Pawlow (l. c.). Inasmuch as the HCl is a stimulant to pancreatic secretion, we may assume that“ anything which stimulates the secretion of HCl in the stomach will also enhance the digestive power of pancreatic juice. (5) It was found that the absence of bile from the duodenal contents — catarrhal icterus — reduces the power of the pancreatic ferments if they are still secreted; such a case was already described in the preceding, where the common gall-duct was stenosed by a small calculus. (6) There exists a compensatory arrangement whereby the alkalinity of the pancreatic juice increases as the acidity of the gastric juice increases, and reversely the alkalinity decreases as the acidity of the gastric juice decreases. These results have been mentioned merely to show the possibilities of this method and the large amount of work yet to be accomplished in this direction. The experiments are still in progress and will be published later.“

Dabei ist zu berücksichtigen, dass diese Ergebnisse von uns im Jahre 1895 vor dem Medizinischen Verein der Johns Hopkins Universität demonstriert wurden, und dass die Methodik und der Plan der physiologischen Fragestellungen im *Johns Hopkins Medical Bulletin* im April 1895 veröffentlicht sind. Dieselben



sind auch in meinem Lehrbuch der Magenkrankheiten 1897 zu finden. (Diseases of the Stomach. 1. Aufl. S. 55. 1897.)

Seither ist es mir zur Pflicht geworden, viele Schüler in dieser Methodik zu unterrichten. Nach und nach habe ich sie jedoch viel weniger gebraucht — eben weil sie sich für pathologische Fälle äusserst selten eignet — und zum Studium der *Physiologie* des Pankreassekrets und des Duodenums gibt es viel genauere und dem Physiologen beliebtere Methoden.

Nicht zu vergessen ist, dass Dr. *Fenton B. Turck* von Chicago im Jahre 1896 einen kurzen Bericht veröffentlichte, in welchem er einen Fall beschrieb von erfolgreicher Intubation des Duodenums mit einer Metallspiralsonde. Physiologisch-pathologische Befunde hat Herr Dr. *Turck* nicht angegeben. Trotz aller dieser Bestrebungen, welche schon vor 15 Jahren eingesetzt haben, und trotz wiederholter Veröffentlichungen der Methodik, die von *F. Kuhn* mit bewunderungswürdigem Fleiss ausgearbeitet worden ist, beginnt der Artikel von *Einhorn* und *Rosenbloom* mit folgenden Worten (l. c. S. 186: veröffentlicht Okt. 1910).

„Früher bestand die einzige Methode, die Sekretion des Pankreas zu studieren, darin, dass man eine temporäre oder permanente Fistel anlegte. Kürzlich hat einer von uns „Eine praktische Methode, den menschlichen Duodenalinhalt zu untersuchen“ beschrieben, welche letzteren der Analyse zugänglich macht.“ Wer diesen Artikel allein liest, gewinnt den Eindruck, als ob dies die erste derartige Methode sei, die je veröffentlicht wurde, und in seinen folgenden Angaben ist weder von *Turck*, *Kuhn* noch von meinen physiologischen Befunden irgendwo die Rede. Es ist nicht immer wünschenswert, dass man bei jedem kurzen Bericht eine Geschichte des Vorangegangenen auf demselben pathologischen und physiologischen Gebiete zitiert. Bei einigen Journalen ist das sogar ausdrücklich unerwünscht. Hat man aber auf die Erzählung der geschichtlichen Entwicklung des Problems verzichtet, und wird nichts von früheren Arbeiten berichtet, so muss man sorgfältig darauf bedacht sein, dass man nicht den Eindruck hinterlässt (wie in diesem besonderen Artikel von *Einhorn* und *Rosenbloom*, l. c.), dass früher überhaupt noch nichts auf diesem Gebiete geleistet worden ist.

Zwar gibt *Einhorn* im Archiv für Verdauungskrankheiten, Bd. XV, S. 199 an, dass ein direktes Einführen von Schläuchen durch den Pylorus von mir und *Kuhn* versucht wurde (?), doch hätte sich das Verfahren nicht bewährt! Wer sich von der Be-



währung der *Kuhnschen* Methode überzeugen will, wird keine Schwierigkeiten haben — was die meinige anbetrifft, so habe ich diesen Punkt schon beleuchtet.

Tatsache ist, dass meine im Johns Hopkins Hospital Bulletin veröffentlichte Arbeit im April 1896 die allererste war, in der überhaupt eine Duodenalintubation als systematische Methodik beschrieben wurde, und die in meinem Buche „*Diseases of the Stomach*“, 1. Aufl. 1897 l. c. angegebenen Befunde brachten, die ersten physiologischen Tatsachen, die am menschlichen Duodenum und Pankreas auf mechanischem Wege erreicht wurden.

Wir kommen zu der wichtigen Frage, ob die neueren Methoden der Duodenalintubation überhaupt etwas Neues zur Pathologie und Physiologie des Duodenums und des Pankreas beitragen können, was nicht auf anderen und exakten Wegen sicherer und objektiver erreicht werden könnte.

Zwischen Herrn Kollegen *Einhorn* und mir selbst bestehen die freundschaftlichsten Beziehungen, er wird es daher nicht übelnehmen, wenn ich für mein Institut die ersten wissenschaftlichen Bemühungen zur Duodenalexploration nochmals in Anspruch nehme, nicht nur das, sondern auch die ersten methodisch erlangten physiologischen Befunde am Menschen. Es ist das, wie sich schon herausgestellt, ein historischer Wendepunkt in der Duodenalphysiologie und -pathologie, dem noch viele ähnliche Arbeiten, wie die von *Kuhn* und *Einhorn*, nachfolgen könnten.

Der neue von *Einhorn* vorgeschlagene Apparat (Berliner klin. Wochschr. 1910, Nr. 12) kann ohne Schwierigkeit in jedem klinischen Laboratorium hergestellt werden. Eine Aspirations-spritze und ein 80—90 cm langer dünner Gummischlauch, welcher am unteren Ende eine Metallkapsel trägt, ist alles, was nötig ist. Grundbedingung von *Einhorns* Duodenalintubation ist, dass eine Magenperistaltik eintritt, welche die Kapsel samt einem Teil des Schlauches durch den Pylorus in das Duodenum schiebt. Das geschieht auch, wenn die *gastrische* Peristole normal ist — manchmal nach langem Warten auch bei etwas verlangsamter Magenperistaltik. Bei Gastrectasien ist es eine schwere Geduldprobe und gelingt in der Regel gar nicht. Bei den verschiedenen Atonien nimmt die Prozedur viel Zeit in Anspruch. Bei narbiger Stenose des Pförtners — Pyloro-Spasmus, Karzinom — Kompression des Pylorus oder Verzerrung des Duodenum durch Pericholecystitis darf man einen Erfolg kaum erwarten. Man kann auch mit der Radiographie solche Zustände zum Teil besser studieren und durch

Analysen des Stuhles Belehrung finden über den Zustand des Pankreas, Methoden, die von *Ad. Schmidt, Holzknecht* u. A. schon ausgebaut wurden.

Also, es gibt pathologische Zustände genug, in welchen sich die neue Methode nicht bewährt, ja nicht einmal das leistet, was die viel erprobtere *Kuhnsche* Methode bietet.

Dadurch, dass die *Einhornsche* Methode der Peristaltik bedarf, muss ja unvermeidlich stets etwas Magensaft einschliesslich HCl (wenn anwesend) mit der Kapsel in das Duodenum dringen. Daher kommt es, dass *Einhorn den Duodenalsaft fast stets neutral findet*, ja 10 mal sogar sauer findet, während *Glaessner, Schumm* und ich denselben *stark alkalisch gefunden haben*. Die Alkaleszens rührte von Karbonaten her. Die *Kuhnsche* und meine eigene Duodenaltechnik hängt nicht von der gerade vorhandenen Peristole ab, sondern man kann mit dem Instrument des Dr. *Franz Kuhn*, vorausgesetzt, dass keine Stenose existiert, willkürlich das Duodenum intubieren. Und je rascher die Passage durch den Magen sich vollzieht, desto geringer wird die Gelegenheit sein, bedeutende Quantitäten sauern Magensafts in das Duodenum zu schieben. Bei der *Einhornschen* Methode geschieht das unvermeidlicherweise durch eine natürliche Magenperistaltik. Nun ist es ein Grundsatz exakter Forschung, alle zu untersuchenden Säfte so isoliert oder vielmehr rein wie nur möglich zu erhalten. Jedoch erhält man nach *Einhorn* eine Mischung von 4 Verdauungssäften: 1. Magensaft, 2. Pankreassaft, 3. Sekret der *Brunnerschen* und *Lieberkühnschen* Drüsen, 4. Galle. Interessant ist es immerhin, die Resultate zu studieren, die mit diesem Gemisch erhalten wurden. Die gegenseitige chemische Koordination dieser Säfte lässt sich auf diese Weise nicht erlernen. Namentlich ist die Beimischung unphysiologischer Mengen von Magensaft für die Pankreasfermente unvorteilhaft, denn normalerweise gehen beim Menschen sehr geringe Quantitäten Mageninhalt auf einmal in das erste Darmsegment und durch den Pylorusreflex sind diese Quantitäten den zuweiligen im Zwölffingerdarm anwesenden Mengen von Pankreassaft und Galle etc. angepasst. Die physiologische Chemie des Duodenums, sowie die nervösen und mechanisch-dynamischen Energien, die hier walten, bilden ein Gebiet der Forschung, wie sie reichhaltiger und mannigfaltiger in der ganzen Biologie nicht vorgefunden werden können.

Enthält der Magen feste Speisen, die erst durch den Magensaft verflüssigt werden, so sind die Portionen, die durch eine gastrische

Kontraktionswelle (i. e. Zusammenziehung des Antrum Pylori) in den Darm gespritzt werden, klein. Im Durchschnitt nicht mehr wie 0,8 bis 1 cm beim Hunde (*Pawlow*, „*Ergebnisse der Physiol.*“, 1902, S. 72). Diese kleine Menge jedoch, wenn sie einmal im Duodenum ist, ruft einen Pylorusverschluss hervor und nach *O. Cohnheim* (Die Physiologie der Verdauung, S. 17) macht sich die Wirkung des Pylorusreflexes so geltend, dass etwa jede zweite Welle den Pylorus verschlossen findet. Die reciproke ehemisch-dynamische Koordination zwischen Duodenalinhalt und Pylorusreflex ist, seit *Hirsch* 1892 diesen Reflex entdeckt hat, von vielen Physiologen und Klinikern erforscht worden. Wichtige Endresultate dieser Experimente und klinischen Beobachtungen sind 1.<sup>o</sup> dass der Pylorus nie dauernd offen bleibt; 2. dass die Menge der gastrischen Entleerungen minimal sind (0,8 bis 1 cm); 3. dass der Chemismus des Duodenum gestört wird durch Verhinderung des Pylorusreflexes.

Deshalb kann man am Menschen durch Intubation nie solche dem Normalen am nächsten stehende Begebnisse sehen wie am operierten Tiere.

Im Jahre 1908 beschrieben *Harry Adler* und ich die physiologisch-chemischen Eigenschaften des Inhaltes einer Pankreascyste (Chemical and physiologic study of Pancreatic cyst fluid by *Hemmeter and Adler*, New York Medical Record, Aug. 6, 1898).

In diesem von Prof. *L. McLane Tiffany* operierten Falle blieb eine offene Fistelbahn bestehen, welche von diesem Chef unserer Chirurgischen Klinik in einem Anhang des erwähnten Artikels beschrieben ist. Durch diesen Sinus schied sich monatelang nach anscheinender Heilung ein Saft aus, der sehr zerstörend auf die Epidermis wirkte und sich später als reiner Pankreassaft ergab.

Mittels eines kleinen Gummikatheters konnte man nach vorangegangenen diätetischen Reizen diesen Saft rein entziehen. Er härtete sich dem von *Glaessner* beschriebenen.

Wir haben von diesem seltenen Fall nichts weiter veröffentlicht, eben weil *Glaessners* schöne Arbeit fast alles, was neu war, schon ziemlich vollständig gebracht hatte. Aber auch, weil dieser Fall einen Privatpatienten betraf, der nicht zu überreden war, sich diesen vielversprechenden Untersuchungen hinzugeben. Zudem wuchs die Fistel zuweilen spontan zu, blieb monatelang anscheinend verheilt, um dann wieder spontan aufzubrechen, gewöhnlich nach Diätfehlern.



Ganz einwandfrei ist in den, in meinem Handbuch der Darmkrankheiten vor zehn Jahren berichteten Untersuchungen bewiesen (Diseases of the Intestines. Vol. I. S. 271. 1901), dass die Bildung des Pankreassaftes von dem chemischen Reiz der Salzsäure bis zu einem gewissen Grade abhängt. (Die „*Enterokinase*“ war von *Schepowalnikoff* im Jahre 1898 aber in einer russischen Dissertation beschrieben worden. — Das *Sekretin* von *Baylis* und *Starling* aber erst 1902 im British Journal of Physiology.) In der deutschen Übersetzung von *Pawlow's* Arbeit der Verdauungsdrüsen war aber schon die Beziehung der HCl des Magensaftes zum Pankreassekret angegeben.

Die Variation der amylytischen Kraft bei verschiedener Nahrung war noch nicht beschrieben worden, ebensowenig beim Menschen die Beeinträchtigung der Wirkung des Pankreasferments durch Abwesenheit von Galle, noch die reziproke Beziehung zwischen der Alkalinität des Pankreassaftes und der Azidität des Magensaftes.

Die *Einhornsche* Duodenalintubation hat einen Vorteil, welcher in gewisser Beziehung einen Fortschritt bedeutet.

Dadurch, dass die Kapsel durch die *gastrische* Peristole in das Duodenum geschoben wird, ist die Technik die denkbar einfachste. Die Kapsel und der kleine Schlauch finden ihren Weg von selbst, wenn die Peristole genügend vorhanden ist. Dem Menschen, der untersucht wird, ist eine unangenehme Prozedur erspart. Das ist ein entschiedener Vorteil, der trotz des Zeitverlustes dieser Methode nicht zu unterschätzen ist.

Da es möglicherweise ebenso viele Instrumente zur Duodenalintubation geben wird wie zur Oesophagoskopie oder zur Gastroskopie, wird es nötig sein, die Vor- und Nachteile und die speziellen Indikationen eines jeden Apparates zu erklären.

Die *Einhornsche* eignet sich in Fällen, bei welchen man sich auf die Peristole verlassen kann, bei welchen man in möglichst einfacher Weise vorgehen muss, um dem Patienten Unannehmlichkeiten zu ersparen, bei welcher man von Anfang an auf die Diagnose von Stenosen und Spasmen verzichtet, und es schliesslich nicht auf die Dauer des Versuches ankommt.

Die *Kuhnschen* Instrumente sind vorzuziehen, wenn man ohne Zeitverlust sicher die Passierbarkeit des Pylorus ausfinden will. Da diese Methode keiner speziellen Mahlzeit bedarf, kann man sie vorzugsweise bei leerem Magen ausführen, wodurch auch



vermieden wird, dass Magensaft in das Duodenum in unphysiologischen Mengen eindringt. Um eine Pankreassekretion zu bewirken, kann man durch die Röhre irgendeinen physiologischen Reizer direkt in das Duodenum einführen.

Oder man kann die Entleerung des Magens abwarten (vorhergegangene Beurteilung oder Radioskopie) und hinterher intubieren.

Bei der Bemerkung, dass das Experiment am Menschen soweit noch nichts Neues geliefert hat, denke ich an die Literatur seit *Glaessners* und *Schumms* schönen Arbeiten. Aber am vorliegenden Fall von Pankreasfistel nach Pankreascysten-Operation ist es geglückt, doch noch eine neue Beobachtung zu machen, nämlich die „*psychischen oder Appetits-Pankreassafts beim Menschen*“.

Nach vielen, zum Teil widersprechenden Resultaten betreffs des Einflusses von Vagusreizung auf die Sekretion des Pankreas (siehe *Nagels* Handbuch der Physiologie des Menschen, Bd. II, S. 737) ist es *Pawlow* gelungen, in einwandfreier Weise den Einfluss dieses Nerven zu demonstrieren (Arch. f. Anat. u. Physiol. 1893).

Ein positiver Erfolg konnte mit diesen Nerven, welche auch früher, jedoch mit negativem Ergebnis gereizt worden waren, dank einer besonderen Versuchsanordnung, welche die auf die Drüse durch den operativen Eingriff am Tiere ausgeübte deprimierende Wirkung vollkommen ausschloss, erzielt werden. So ist es *Pawlow* gelungen, vom Vagus eine reichliche, vom Sympathikus eine spärliche Pankreassekretion zu erhalten. Also Vagusreizung kann Pankreassekretion hervorrufen. Wie verhält sich die psychische Absonderung dieses Saftes?

Wie wir wissen, ruft die Gegenwart von Salzsäure im Duodenum starke Pankreassekretion hervor. (Nach *Bayliss* und *Starling* durch vorherige Bildung des Hormons *Sekretin*). Da nun aber sowohl Vagusreizung wie auch der Appetit (Psyche) vorerst Magensekretion hervorrufen, musste man entscheiden, ob es überhaupt eine rein psychische Pankreassekretion gebe.

Diesen Beweis brachte die schöne Entdeckung von *Papielski* (Dissertation St. Petersburg 1896). Die entscheidende Beobachtung wurde dadurch erbracht, dass nach Reizung des Vagus beim Hunde dem Übergange des sauren Mageninhalts in das Duodenum vorgebeugt wurde, wobei das Ergebnis dasselbe war. Reizung des Vagus brachte Pankreassekretion hervor, selbst wenn keine Salzsäure in das Duodenum eindrang, es war demnach ein reiner Nerveneffekt.

Des weiteren hat *O. Cohnheim* auf eine reine psychische Pankreassekretion angespielt (Münchener Med. Wochenschr. 1907—2581). Er beschreibt nämlich, dass Hunde 1 bis 1½ Stunden nach Nahrungsaufnahme, also ehe etwas in den Dünndarm kommt, eine 10—30 Minuten dauernde Pankreassekretion beobachten lassen. Die Beobachtung wäre einwandfrei, wenn sie an einem Tier angestellt worden wäre, bei welchem durch Operation der Magenchymus nach aussen geleitet worden wäre, und bei welchem zugleich auch eine Pankreasfistel angebracht war. Es ist denkbar, dass bei normalem Magen etwas Magenchymus in das Duodenum treten konnte und sehr minimale Quantitäten (1 Tropfen) können zur Bildung des Sekretins führen.

Bei dem Patienten mit Pankreasfistel lag die Sache einfacher. Er hatte Tage, ja Wochen, in welchen er bei zahlreichen Probemahlzeiten durchaus keine Salzsäure noch Fermente zeigte, und das bei erhaltenem Appetit, um dann später eine normale Sekretion des Magens zu offenbaren.

Diesen Zustand von extremem Wechsel der Qualität des Magensafts habe ich zuerst beschrieben und mit dem Namen „*Heterochylia*“ belegt. Es ist das in der Regel eine Magen-neurose, kann aber auch von wechselnden Zuständen der die Magen-sekretion anregenden Hormone herrühren. Dabei will ich nicht in Abrede stellen, dass es psychische inhibitorische Vaguseinflüsse geben kann, die sich erst beim Experiment äussern und an die man denken muss selbst bei der einfachen Entnahme einer Probemahlzeit, und noch viel mehr bei der Duodenalintubation.

Die ehemischen Beziehungen der *Heterochylia* und *Achylia gastrica* zur *Pankreas-Insuffizienz* habe ich beschrieben in „*American Medicine*. Vol. IX., p. 398—401. März 1905. „*Advances in the Physiol. and Pathol. of the Pankreas and their Application to the Diagnosis of Pancreatic Diseases*.“

Wenn bei unserem Pankreasfistelträger während der *Achylia gastrica*-Periode ein Hungerzustand veranlasst war, und danach eine psychische Erregung des Appetits erzeugt wurde, ergab sich regelmässig eine Sekretion von Pankreassaft, und zwar gewöhnlich 2 bis 4 Minuten nach der Appetitserregung. In drei verschiedenen Versuchen konnten wir finden, dass dies qualitativ wie quantitativ der intensivste Pankreassaft war, welcher überhaupt von diesem Manne erhalten werden konnte; mit einer Beschränkung — wir konnten ihn nämlich nicht zu Experimenten überreden,

genügend an Zahl, während er normalen Magensaft sezernierte, noch zum Einnehmen von Salzsäure zu bewegen.

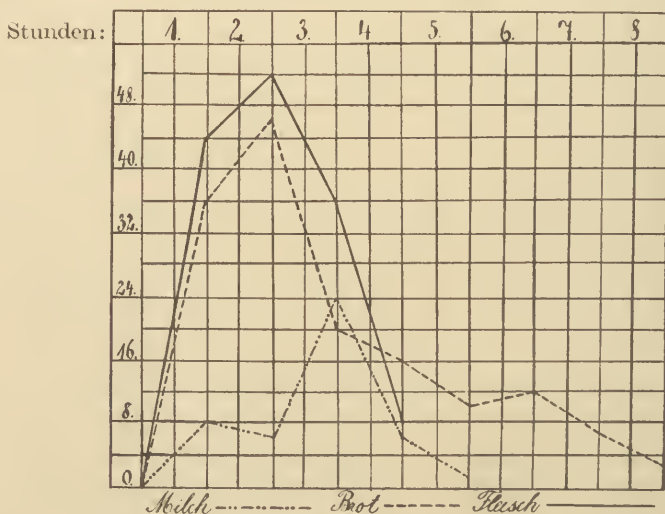
Die wenigen Versuche während normaler Magensekretion (vier Beobachtungen), zeigten jedoch, dass der dabei abgeschiedene Pankreassaft nicht effektiver war als der psychische Pankreassaft.

Dabei war er stets bestrebt, auf eine permanente Verheilung der Fistel hinzuarbeiten, die auch schliesslich gelang. Nach letzten Berichten ist die Öffnung nun schon seit acht Monaten geschlossen, und der Mann bei bestem Wohlsein.

Es ist noch beizufügen, dass das Drainrohr dieses Kranken in einer kleinen Erweiterung des Ductus Pancreaticus lag, denn man bekam fast nie die Galle in dem Ausfluss. *Glaessners* Patientin konnte 8 Tage kontinuierlich beobachtet werden.

Da unsere Ergebnisse die Höhepunkte der Sekretion betreffen, welche bei verschiedener Nahrung beobachtet wurden, von denen *Glaessners* etwas abweichen, füge ich eine zusammengesetzte Kurve bei, welche die Menge und verdauende Kraft des Pankreas-Sekrets graphisch illustriert. Im ganzen genommen sind diese Kurven als eine Bestätigung der Resultate *Glaessners* zu betrachten.

*Alkaleszenz.* War die Gesamtazidität des Magensafts normal,



so betrug die erforderliche Menge  $\frac{N}{10}$   $H_2SO_4$ , um 10 cem Pankreassaft zu neutralisieren, 3,5 bis 5 cem. Als Indikator diente Phenolphthalein: war die Acidität des Magensafts hoch, so stieg auch die

Alkaleszenz des Pankreassafts, jedoch nicht proportional. Sank die Acidität des Magensafts, so war die Alkaleszenz des Pankreassafts niedriger, doch konnte auch hier keine korrespondierende Eroportion erkannt werden; um dies genau zu entscheiden, ist das Tierexperiment unbedingt nötig. Denn man kann dann durch Pingegeben von bestimmten Quantitäten HCl die Acidität des Magensafts variieren, durch Alkalien die frei HCl eventuell binden und den Effekt auf die Alkaleszenz des Pankreassafts studieren.

Interessant ist es zu bemerken, dass nach Kohlehydratkost und gemischter Diät die Pankreassekretion sofort beginnt, während nach Fett und Eiweiss mindestens eine Stunde verläuft, ehe sie beginnt. Unzweifelhaft hängt das von der Geschwindigkeit ab, mit welcher diese verschiedenen Nahrungen durch die gastrische Peristole in das Duodenum befördert werden. Brot und gemischte Diät verlassen den Magen rascher wie Fett und Fleisch (Cannon American Journal Physiol. 12, p. 387, 1904). Schon 1899 hatte *Walther* gezeigt, dass die Quantität der Pankreassekretion von dem chemischen Charakter der Nahrung abhängt (Archives d. Sciences biol. 7, I, 1899.). — Also sind die Resultate von *Glaessner* und mir als Bestätigung des Tierexperiments anzusehen.

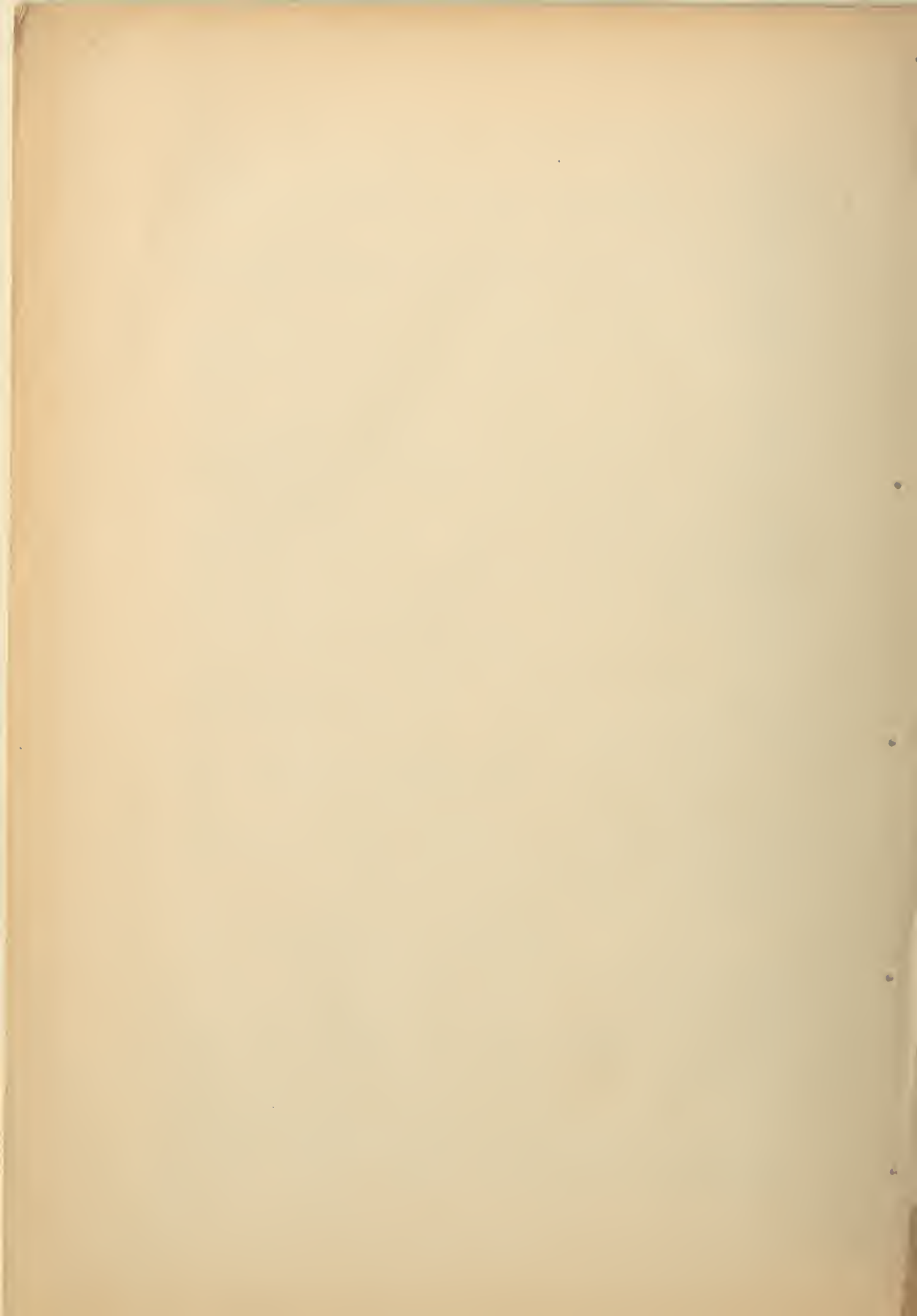
Das Sekret war klar und die Quantität wechselte von Mahl zu Mahl, war am reichlichsten nach gemischter Diät (Brot, Fleisch, Kartoffelbrei, Milch), hier wurden 780 ccm in drei Mahlzeiten an einem Tag sezerniert.

Nach Fett war die sezernierte Diät am geringsten, z. B. 410 ccm nach reichlichem Rahm oder Olivenöl. Brot allein oder Kartoffelbrei bewirkte am Tage ungefähr 500 cm Sekret. Es ist mir nicht gelungen, trotz vieler Versuche, Milch zur Gerinnung zu bringen mit irgendeiner Probe dieses Sekretes, noch ein Proferment des Labs nachzuweisen.

Wenn das Sekret absolut rein gewonnen wurde, so zeigte sich eine geringe — fettspaltende — eiweissverdauende und stärkeverdauende Kraft — wie wenn es mit Galle vermischt kam oder später mit Galle versetzt wurde, wenn auch nicht in demselben Grade wie von *Bruno* angegeben wird (Archiv de Sciences biol. de St. Petersburg, 1899). Mit der Lipase dieses Pankreassekrets aber ist die Reaktion so viel intensiver mit Galle gewesen, dass wir darin auch eine Bestätigung der Ansichten gefunden haben, welche in den gallensauren Salzen einen Aktivator dieser Lipase erkennen (*Nencki — Zuntz — Pawlow — Magnus — Zeitschr. f. physiol. Chem.* 48, 376, 1906).

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Anleitung

zur

# Diagnostik der Abdominaltumoren

## unter Zugrundelegung der Palpation

Eine klinische Erläuterung zur Palpation des Abdomens

von

**Prof. Dr. G. L. Sacconaghi**

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Preis broch. 12 M., gbd. 13,60 M.

**Schmidt's Jahrbücher:** . . . Noorden sagt in der Vorrede des ihm gewidmeten Buches, die Palpation stände in der Praxis allem Anderen voran, und er hat sicherlich recht. Darum wollen wir dieses Buch gern und mit Dank entgegennehmen, in dem ein augenscheinlich besonders geschickter, sorgsamer und erfahrener Untersucher klar und anschaulich zusammenstellt, was man alles fühlen und wie man es richtig verwerten kann.

Der Titel ist etwas zu knapp gefasst. S. bespricht zunächst die Palpation des Unterleibes und seiner einzelnen Organe im allgemeinen. Dann kommen scheinbare Tumoren, „Phantomtumoren“; dann die Bauchtumoren im allgemeinen, dann Ascites, dystopische Organe, und dann nimmt S. erst die einzelnen Organe und Gegenden des Unterleibes durch, dabei nicht nur etwaige Neubildungen, sondern auch sonstige fühlbare Veränderungen eingehend berücksichtigend. Und da ausser der Palpation auch über die anderen Untersuchungsmethoden mancherlei gesagt ist, so stellt das Ganze ein inhaltsreiches, wertvolles Buch dar, wohl geeignet, uns auf einem besonders schwierigen und besonders wichtigen Gebiete der Diagnostik zu raten und zu helfen.

**Zentralbl. f. inn. Medizin:** . . . Ein ausserordentlicher Fleiss in der Sammlung des Materiales und eine nicht geringere Sorgfalt und Gewissenhaftigkeit in dessen Sichtung und Beurteilung sprechen von jedem Blatte, und dabei stösst man überall auch auf den reichen persönlichen Erfahrungsschatz des Verf.s. — Das Werk bietet eine solche Fülle der Belehrung, und in so bequemer, übersichtlicher Form, dass es, wenn erst bekannt, auch vielen deutschen Aerzten ein unentbehrlicher Wegweiser auf diesem schwierigen Gebiete werden wird. — Die von Plitek besorgte gewandte Uebertragung ermöglicht einen ungekürzten Genuss bei der Lektüre des trefflichen Buches.

Medizinischer Verlag von S. KARGER in Berlin NW. 6.

# **Die methodische Intestinalpalpation**

mittels der

**topographischen Gleit- und Tiefenpalpation**

**und ihre Ergebnisse**

mit Einschluss der Ileocoecalgegend und mit  
Berücksichtigung der Lageanomalien des Darmes.

Von

**Dr. Theodor Hausmann**

(Orel)

Mit 9 Abbildungen im Text und zwei Tafeln. Lex. 8°. Brosch. M. 4,50.

**Archiv f. Verdauungskrankheiten:** . . . Nach sorgfältiger und wiederholter Lektüre des kleinen Werkes kann ich ohne Uebertreibung sagen, dass es eine wissenschaftliche Tat bedeutet. Ich will ganz davon absehen, dass es von einem den Zentren der Wissenschaft fernstehenden Arzte geschrieben ist, obwohl auch dies etwas bedeutet. Aber mehr als das, es ist von einem methodischen Geiste durchweht, dem wir heute nicht allzu oft begegnen.

Auf die Einzelheiten der Intestinalpalpation einzugehen oder, was noch verlockender wäre, mit dem Autor über die Schwierigkeiten der Deutung zweifelhafter palpatorischer Befunde zu diskutieren, müssen wir uns aus Raumangel versagen. Nur das eine habe ich aus der Hausmannschen Monographie ersehen und werden auch die anderen Leser des Buches ersehen, dass wir in bezug auf die Intestinalpalpation auf Grund der Hausmannschen Lehren alle unzulernen haben, und dass in Zukunft andere, höhere Ansprüche an eine sachgemäße methodische Gastrointestinalpalpation an uns herantreten werden. Dem Autor wird jedenfalls das Verdienst nicht abgesprochen werden, dass er die Intestinalpalpation durch sorgfältige und fleissige Übung auf diesem Gebiete unbedingt auf eine höhere Stufe gebracht hat.

Einer besonderen Empfehlung bedarf das Hausmannsche Werk nicht weiter, es spricht für sich selbst. Boas.

Von demselben Verfasser ist in meinem Verlage ferner erschienen:

## **Ueber das Tasten normaler Magenteile.**

Nebst Bemerkungen zur Höhenbestimmung der Bauchorgane.

Lex. 8°. Brosch. M. 1.—.

**Deutsche Mediz. Wochenschr.:** Eine sehr verdienstliche Arbeit, die die Bedeutung der Palpation, unserer wichtigsten Untersuchungsmethode, die leider auf Kosten anderer vielfach vernachlässigt wird, ins rechte Licht rückt. . . .

**Münchener Mediz. Wochenschr.:** . . . Es ist dies ein für den Wert der Tiefenpalpation doch genugsam sprechender Erfolg.

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**Kritische Glossen eines Klinikers**

zur

## **Radiologie des Magens.**

Von

**Prof. Dr. B. STILLER**

in Budapest.

Lex. 8°. Brosch. M. 1,20.

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Medizinischer Verlag von S. KARGER in Berlin NW. 6.

Reprinted from the New York Medical Journal for  
June 24, 1911.

IN MEMORIAM—CHRISTIAN A. HERTER.

By JOHN C. HEMMETER, M. D., Phil. D., LL. D.,  
Baltimore.

Professor of Physiology in the University of Maryland.

Goethe once classified the various kinds of nature contemplation in a comprehensive way: First, the lowest grade is represented by the *Nutzensuchenden*—the utility seekers—who apply that which Nature offers for their utilitarian purposes. The second are the *Wissbegierigen*—or those simply eager for knowledge—the “curious for Nature.” The third are the *Anschauenden*—who seek to avoid imagination as far as possible and reduce everything to intuition (from the Latin *intueri*, to look on or into). The fourth group are the *Umfassenden*—these minds operate in the opposite manner from the intuitionists, for they start from preconceived ideas and seek to encompass (*umfassen*) their problem by a seeking of a realization of their ideas in Nature.

This classification is a helpful one in endeavoring to understand great minds like that of Herter.

Christian A. Herter died December 5, 1910, in the forty-sixth year of his age, at his residence in New York, of pneumonia. At the time of his death he was Professor of Pharmacology and Therapeutics in Columbia University, New York.

Through his death, scientific medicine has suffered a profound loss, for not only was the manifold character of his scientific activity astonishing and crowned with the most felicitous results, but, in addition, Herter was a philanthropist in the strict sense of that term—for we must distinguish between philanthropy in a strict sense and in a gen-



eral sense when considering great men such as he was.

Philanthropy in the strict sense I designate as that which can help only by material gifts—the founding of institutions, hospitals, and academic chairs, etc.—by the latter term I refer to a philanthropy which benefits mankind through the effects of intellectual effort, by special scientific activity.

In both of these respects Herter was a philanthropist. Because he had means it was possible for him to establish lectureships in the University and Bellevue Hospital Medical College, New York, and the Johns Hopkins University in Baltimore. Through these it became possible to call the most advanced thinkers in scientific medicine and the allied sciences annually to these institutions.

He maintained in New York a private laboratory for physiology and chemistry. It was also only through his financial support that the *Journal of Biological Chemistry* could be founded and maintained. He was, therefore, a practical philanthropist in the strict sense of the term. But the greatest benefits will prove to be those of his intellectual creations, for his many works in the fields of biological chemistry, pathology, pharmacology, and chemical medicine give evidence of an enthusiastic and talented investigator.

His sense of duty to the public welfare was shown by his accepting public duties of responsibility without thought of compensation. He was a member of the first board of directors of the Rockefeller Institute for Medical Research in New York, treasurer of that institute, and consulting physician of the new hospital recently added. He also accepted the position of scientific referee at the invitation of the United States Government, becoming a member of the Referee Board of the United States Department of Agriculture. This tribunal consisted of five counsellors appointed by the President to accomplish the proper administration law regulating foods and chemical products.

Hemmeter: Christian A. Herter.

Herter was born in 1864, at Glenville, Conn., received an academic education in New York and the degree of Doctor of Medicine from the College of Physicians and Surgeons, in 1885. He was an industrious writer, and space is lacking except to enumerate the more important of his publications. In 1890 he published a work on the *Diagnosis of Nervous Diseases*, and in 1902 his *Lectures on Chemical Pathology*. In more recent years he was especially interested in *Autointoxications from the Digestive Tract*, in which field he completed noteworthy bacteriological and chemical studies.

As collaborator in the *International Contributions to the Pathology and Therapy of Disturbances of Nutrition* (Berlin), he contributed a fine piece of work to the first volume (p. 275). This contribution on *Experimental Variation of Intestinal Flora by Changes of Diet* was one of his last works.

In his inspiring book *Great Men*, Wilhelm Ostwald divides the great investigators into two groups: 1, The classicists; and, 2, the romanticists. They are distinguished by the differences in the reaction times of their minds. The classicists are the slow ones, the romanticists the more rapid. The classicists are the thorough, penetrating, objective workers, who exhaust their problems. The romanticists are the subjective workers, who, according to Goethe (*die Umfassenden*, he calls them), would bound the multiplicity of their problems by the limits of their own ideas. They are more frequently guided by preconceived ideas, are not so thorough, but have great wealth of thought. This superfluity of ideas, in fact, determines the mental pulse rate. For this reason the romanticists, such as Davy, Liebig, Benjamin Thompson (Count Rumford), cannot be so exhaustive as the classicists, because they undertake too many problems and are diverted from the same degree of concentration by the superabundance of their conceptions.

In his sixteenth aphorism, Heraclitus expressed this as follows: πολλὰ ὑμαθίη νόον ἔχεν ὃν διδάσκει,

i. e., Much knowledge does not lead to understanding. This expression does not strictly apply to the great romanticists, for their services have often led to a deep insight.

Was Dr. Herter a classicist or a romanticist? I knew him well, personally, and have eagerly read his works, but must acknowledge being at a loss how to place this man in Ostwald's classification. He produced much and rapidly, his intellectual reaction was quick, he possessed a remarkable wealth of ideas, and was filled with enthusiasm. These are characteristic of the romanticist.

On the other hand, he lacked certain characteristics of the romanticist—for he was thorough, not superficial, he did not allow himself to be led by *a priori*, i. e., intuitive, conceptions; he belonged to Goethe's *Anschauenden*, contemplative, believing that all experience comes from contemplation.

It remains to be recorded that Christian Herter was endowed with an artistic temperament. He was a technically developed violoncellist, and it often appeared to me that his musical accomplishment rose to virtuosity. It was my personal privilege occasionally to accompany him on the piano. Unforgettable are the evenings in Herter's home when the physiologist, Jacques Loeb, Herter, and I, after a discourse on physiological topics, enjoyed the relaxation afforded by the compositions of Beethoven and other master musicians.

A great heart, beating warmly for its fellowmen, has been stilled, a profound thinker has found peace; an artist in scientific technique, as well as music, has been called to participate in the "harmony of the spheres." According to Hippocrates, ὁ μὲν βίος βραχύς, ἡ δὲ τέχνη μακρά, Life is short, but art long.

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**In memoriam**  
**Christian Archibald Herter**  
(1864—1910).

Sonderabdruck aus: Internationale Beiträge z. Pathologie u. Therapie  
der Ernährungsstörungen. Bd. 3. Heft 1.

Redigiert von Prof. Dr. A. Bickel (Berlin).

(Verlag von August Hirschwald in Berlin NW. 7.)

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**In memoriam**  
**Christian Archibald Herter**  
(1864—1910).

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Goethe hat einmal die verschiedenen Arten der Naturbetrachtung in übersichtlicher Weise eingeteilt. Die tiefste Stufe sind die Nutzenden, die Nutzen-Suchenden, die das, was die Natur bietet, für ihre praktischen Zwecke verwenden; die zweite Stufe bilden die Wissbegierigen, die nur das wissenschaftlich verarbeiten, was sie vorfinden; zu der dritten Stufe, den Anschauenden, rechnet sich Goethe selbst; sie suchen die Imagination nach Möglichkeit zu vermeiden und führen alles auf Anschaulichkeit zurück; die vierte Gruppe, die Umfassenden, schlagen den umgekehrten Weg ein, sie gehen von Ideen aus und suchen deren Verwirklichung in der Natur. Hier geht der Verstand, nach Kants Darlegung: „von der Anschauung eines Ganzen als eines solchen, zum Besonderen, das ist, von dem Ganzen zu den Teilen“.

Unsere erste Pflicht bei dem Tode eines jeden bedeutenden Denkers ist ehrfurchtsvoll und sympathisch zu studieren — „wes Geistes Kind er war“.

Christian A. Herter starb am 5. Dezember 1910 in seiner Wohnung, in New York, an Lungenentzündung im 46. Lebensjahre. Zur Zeit seines Todes war er „Professor of Pharmacology and Therapeutics“ an der Columbia-Universität in New York.

Durch seinen Tod hat die wissenschaftliche Medizin einen herben Verlust erlitten, denn nicht nur war die Mannigfaltigkeit seiner wissenschaftlichen Tätigkeit erstaunlich, und von den glücklichsten Resultaten gekrönt, sondern dazu war Herter ein Philanthrop im engeren Sinne des Wortes. Denn wir müssen bei einem grossen Menschen, wie er war, von Philanthropie im engeren und im weiteren

Sinne unterscheiden. Die engere Philanthropie nenne ich diejenige, welche nur durch materielle Gaben — Gründungen von Instituten, Hospitälern, Lehrstühlen — helfen kann. Die weitere Philanthropie nenne ich solche, welche die Menschheit durch die Effekte der geistigen Arbeit, des speziellen wissenschaftlichen Wirkens beglückt.

In beiden Sinnen war er Philanthrop; dadurch, dass er wohlhabend war, wurde es ihm möglich an „the University and Bellevue Hospital Medical College“, New York, und an der „Johns Hopkins Universität“ in Baltimore „Lectureships“ zu gründen, durch welche die jährliche Berufung der bedeutendsten Denker in der wissenschaftlichen Medizin und verwandten Wissenschaften, an jene Institute ermöglicht wurde. Er unterhielt in New York ein Privat-Laboratorium für Physiologie und Chemie. Auch war es nur durch seine finanzielle Unterstützung möglich, das „Journal of Biologic Chemistry“ zu gründen und fortzuführen. Er war demnach tatsächlich ein praktischer Philanthrop im engeren Sinne des Wortes. Doch als seine grössten Wohltaten werden sich die Erzeugnisse seines Geistes bewähren, denn seine vielen Arbeiten auf dem Gebiete der biologischen Chemie, Pathologie, Pharmakologie und klinischen Medizin, geben die Beweise eines begeisterten und talentvollen Forschers.

Sein Pflichtgefühl dem öffentlichen Wohl gegenüber bewies er durch die Annahme öffentlicher Aemter, die ihn mit verantwortlichen Pflichten bürdeten, ohne an die geringste Belohnung zu denken. So war er ein Mitglied des ersten Direktoriums des „Rockefeller-Instituts für medizinische Forschung“ in New York, Schatzmeister dieses Instituts und konsultierender Arzt des an diese Anstalt beigefügtem neuen Hospitals. Er nahm auch die Stellung eines wissenschaftlichen Referenten an, zu welcher er von der Regierung der Vereinigten Staaten eingeladen wurde — nämlich, an dem „Referee Board of the U. S. Department of Agriculture“. Dies Tribunal bestand aus 5 Räten, die vom Präsidenten angestellt wurden, um die richtige Anwendung der Gesetze zu erzielen, welche zur Regulierung der meisten Nahrungsmittel und chemischen Produkte erlassen wurden.

Herter wurde im Jahre 1864 in Glenville im Staate Connecticut geboren, erhielt seine akademische Erziehung in New York und erhielt seinen Doktorgrad von „the College of Physicians and Surgeons“ im Jahre 1885. Er war ein fleissiger Schriftsteller und es würde zu weit führen, selbst nur seine bedeutenderen Publikationen

anzugeben. Im Jahre 1890 gab er ein grösseres Werk über „Diagnosis of nervous diseases“ heraus und 1902 seine „Vorlesungen über chemische Pathologie“. In letzteren Jahren interessierten ihn speziell die „Autointoxikationen des Verdauungstrakts“, auf welchem Gebiete er glückliche bakteriologische und chemische Studien vollendete.

Als Mitherausgeber der „Internationalen Beiträge zur Pathologie und Therapie der Ernährungsstörungen“ hat er sich durch eine schöne Arbeit im ersten Band, S. 275, betätigt. Diese Mitteilung „Experimental Variation of Intestinal Flora by Changes of Diet“ stellt eine seiner letzten Leistungen dar.

In seinem geistreichen Werke „Grosse Männer“ teilt Wilhelm Ostwald die grossen Forscher in 2 Gruppen ein: 1. die Klassiker und 2. die Romantiker. Sie unterscheiden sich durch die Verschiedenheit in der Reaktionsgeschwindigkeit ihres Geistes. Die Klassiker sind die Langsamen, die Romantiker die Geschwinden. Die Klassiker sind die gründlichen, durchdringenden, objektiven Arbeiter, die ihre Probleme erschöpfen; die Romantiker sind die subjektiven Arbeiter, die nach Goethe die Mannigfaltigkeiten ihres Problems mit dem Rahmen ihrer eigenen Ideen umfassen wollen. „Die Umfassenden“. Sie lassen sich von vorgefassten Ideen häufiger leiten, sind nicht so gründlich und erschöpfend, haben aber einen gewaltigen Gedankenreichtum — tatsächlich soll diese Ueberfülle der Gedanken das Tempo des geistigen Pulsschlags bedingen. Deswegen können die Romantiker wie Davy, Liebig, Benjamin Thompson (Count Rumford) nicht so gründlich sein wie die Klassiker, eben weil die ersteren zu viele Probleme unternehmen und durch zu viele Gedanken eine Konzentration in demselben Grade wie beim Klassiker unmöglich ist.

In seinem 16. Aphorismus drückt das schon Heraclitus folgendermassen aus:

*Πολυμαθία νόον ἔχειν οὐκ διδάσκει.*

„Viel des Wissens führt nicht zur Einsicht“. Auf die grossen Romantiker angewandt ist dieser Denkspruch nicht ganz richtig, denn ihre Leistungen haben oft zu tiefer Einsicht geführt. Was war nun Herter? Klassiker oder Romantiker? Ich habe ihn persönlich gut gekannt, und bin ein eifriger Leser seiner Schriften gewesen, muss aber bekennen, dass dieser Mann sehr schwer in Ostwald's Klassifikation einzureihen ist.



Er produzierte viel und schnell — seine geistige Reaktion war geschwind, er hatte eine merkwürdige Gedankenfülle und war von Begeisterung erfüllt — das sind Merkmale des Romantikers.

Auf der anderen Seite gingen ihm bestimmte Charakteristiken des Romantikers ab — er war doch gründlich, nicht oberflächlich — er liess sich nicht von vorgefassten Ideen leiten — er gehörte zu den „Anschauenden“ Goethes und war in dieser Beziehung Klassiker.

Es muss noch erwähnt werden, dass Christian Herter ein künstlerisch begabter Mensch war. Er war ein technisch so geübter Cellist, dass es mir häufig vorkam, als ob seine musikalischen Leistungen an das Virtuosenhafte reichten. Persönlich ist es mir vergönnt gewesen, zuweilen mit ihm zusammen zu musizieren, wobei das Klavier von mir übernommen wurde.

Unvergesslich bleiben mir die Abende in Herters Hause, an welchen der Physiologe Jacques Loeb, Herter und ich nach physiologischen Diskussionen uns den Abend mit Beethoven und Brahmschen Kompositionen verschönerten.

Es ist ein grosses, für die Mitmenschen warmschlagendes Herz zum Stillstand gekommen — ein tiefer Denker ist heimgegangen zum Frieden. Ein Künstler der wissenschaftlichen Technik sowie der Musik ist abberufen zur „Harmonie der Sphären“.

Ὁ μὲν βίος βραχύς ἡ δὲ τέχνη μακρά

(Hippokrates: „Kurz ist das Leben, lang ist die Kunst“.)

**John C. Hemmeter.**





Sonder-Abdruck aus

# Zeitschrift für biologische Technik und Methodik

Unter Mitwirkung von Fachgenossen

herausgegeben von

**Dr. MARTIN GILDEMEISTER**

Professor an der Universität in Straßburg i. E.

**Dr. med. und phil. John C. Hemmeter**, Professor der Physiologie an der Universität von Maryland, Baltimore Md. (Aus dem biologischen Marinelaboratorium des United States Bureau of Fisheries zu Woods Hole Mass.): Zur Technik von Vagusexperimenten am Herzen von *Scyllium*, *Mustelus canis*, *Cynais canis*, *Carcharias littoralis*, *Squalus acanthias*. Mit fünf Figuren . . . . .

**Dr. med. und phil. John C. Hemmeter**, Professor der Physiologie an der Universität von Maryland, Baltimore Md. (Aus dem biologischen Marinelaboratorium des United States Bureau of Fisheries zu Woods Hole Mass.): Methodik der gleichzeitigen Registrierung des Atmungs- und Herzrhythmus beim Selachier . . . . .



LEIPZIG  
VERLAG VON JOHANN AMBROSIOUS BARTH  
1911.



Die „Zeitschrift für biologische Technik und Methodik“ erscheint in zwanglosen Hefen (6—8), die zu Bänden von etwa 25 Druckbogen vereinigt werden. Der Preis des Bandes beträgt *M* 15.—. Der Inhalt zerfällt in:

- I. Originalmitteilungen,
- II. Notizen aus der Arbeits- und Lehrpraxis,
- III. Sammelreferate.

Alle Beiträge erscheinen in deutscher Sprache. In französischer, englischer oder italienischer Sprache eingeschickte Arbeiten werden sorgfältig übersetzt; das Autorenhonorar wird in diesem Falle zur Bestreitung der Übersetzungskosten verwendet.

Die Originalmitteilungen sollen, dem Charakter der Zeitschrift gemäß, das Technische und Methodische biologischer Untersuchungen, Apparate und Verfahren, Kurs- und Vorlesungsversuche u. dgl. enthalten. Ihr Umfang soll im allgemeinen  $\frac{1}{2}$  Druckbogen nicht überschreiten.

In die Abteilung „Notizen aus der Arbeits- und Lehrpraxis“ werden kurze Mitteilungen aus Laboratorien und Instituten über dort erprobte Verfahren und Einrichtungen aufgenommen. Es liegt in der Natur der Sache, daß manches davon keinen Anspruch auf völlige Neuheit wird machen können.

Die Sammelreferate berichten in größeren zeitlichen Abständen über die technischen Fortschritte auf einzelnen Gebieten.

Das Honorar beträgt pro Druckbogen *M* 30.—. Von jeder Arbeit werden dem Verfasser 50 Sonderabzüge kostenfrei geliefert.

Es wird gebeten, die Abbildungen in solcher Ausführung einzuliefern, daß sie photographisch reproduziert werden können (Zeichnungen werden in der Reproduktion gewöhnlich besser als Photographien. Sie sind mit schwarzer Tusche auf weißem Papier herzustellen). Alle Abbildungen werden, wenn irgend möglich, im Text gebracht, nicht auf besonderen Tafeln.

Die Zeitschrift umfaßt alle biologischen Spezialwissenschaften, soweit sie sich des Experiments bedienen (**Physiologie der Tiere und der Pflanzen, physiologische Chemie, Bakteriologie, Serologie, Pharmakologie, experimentelle Pathologie, experimentelle Psychologie, experimentelle Morphologie, Entwicklungs- und Vererbungslehre**).

Die **mikroskopische Technik** (Einbetten, Färben, Schneiden) und die **medizinisch-therapeutische Technik** wird nicht berücksichtigt.

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*Sonder-Abdruck aus*  
**„Zeitschrift für biologische Technik und Methodik“.**  
*1911. Band II. Nr. 5.*  
*Verlag von Johann Ambrosius Barth in Leipzig.*

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(Aus dem biologischen Marinelaboratorium des United States Bureau of Fisheries zu Woods Hole Mass.)

## **Zur Technik von Vagusexperimenten am Herzen von Scyllium, Mustelus canis, Cynais canis, Carcharias littoralis, Squalus acanthias.**

I. Methodik der Präparierung des Ramus cardiacus vagi.

II. Freilegung und Isolierung des Herzens.

Von

Dr. med. u. phil. JOHN C. HEMMETER,

Professor der Physiologie an der Universität von Maryland, Baltimore Md.

(Mit fünf Figuren.)

Für größere Untersuchungen in Marinelaboratorien braucht der Physiologe ein lebendes Material, auf dessen Reichhaltigkeit und Zuverlässigkeit er sich annähernd verlassen kann. Das Versuchsobjekt darf unter der nötigen Technik nicht zu empfindlich, sondern im Gegenteil muß ziemlich lebenszäh und resistent sein. Schließlich ist es wünschenswert, daß sich das Tier in der Gefangenschaft (Aquarien) leicht erhalten läßt. Diesen Ansprüchen genügen die Fische, welche im Titel genannt sind. An den Küsten der Vereinigten Staaten von Maine bis Florida sind es hauptsächlich *Mustelus canis* (the Dogfish) und die Haifische, welche dieses Material liefern, und in den marinebiologischen Laboratorien Europas vertritt namentlich *Scyllium* diese Stelle.

Die größeren Elasmobranchier-, wie die verschiedenen Haifischarten, sind nur zu Ausnahmeversuchen verwendbar, weil sie wegen ihrer Größe schwer zu handhaben und auch sehr schwierig am Leben zu erhalten sind. Es kommen jedoch Probleme vor, wo der größte Hai nützlich wird, wenn man ihn nur lange genug am Leben erhalten kann. Zum Beispiel fand ich dieses Tier dienlich, als ich in einer langen Versuchsreihe dem Problem der chemischen Veränderungen im Herzen nach Vagusreizung näher zu kommen suchte. Es kam darauf an, so viel Trockensubstanz des Herzens wie möglich zu sammeln, erstens von normalen, nicht gereizten Herzen, und zweitens von Herzen, bei denen der Ramus cardiacus vagi bis zum Herzstillstand gereizt wurde.



Das Herz von *Squalus acanthias* oder *Cynais canis* oder von *Scyllium* wiegt bei einem Fisch, dessen Körpergewicht 2 kg beträgt, im Durchschnitt 1,647 g, frisch dem Perikardium entnommen und möglichst von Blut befreit. Vom Sinus venosus kann man nicht viel mit herausnehmen, und die Aorta muß dicht am Bulbus arteriosus durchschnitten werden, beide erst nach Unterlegung von doppelten Ligaturen, so daß die Entfernung des Herzens blutlos geschieht. Der Wassergehalt des Elasmobranchierherzens beträgt 80%, d. h. nur ein Fünftel des frischen Gewichts ist Trockensubstanz, man muß daher an ungefähr 165 Fischen operieren, ehe man 30 g Herztrockensubstanz sammeln kann. Es muß einleuchten, daß ein größeres Tier, wie der Hai (*Carcharias littoralis*, Sand Shark), dem Operateur Mühe und Zeit erspart, speziell bei solchen Untersuchungen, wo es auf die quantitative Bestimmung von Kalium, Natrium, Kalzium und Magnesium — in zwei Serien von Herzen — a) vom Vagus aus gereizten und b) nicht gereizten ankommt. Denn die Quantitäten dieser Substanzen im Herz sind minimal, z. B. für Kalium ( $K_2O$ ) erst 0,38 g auf 100 g fettfreier Trockensubstanz. So wird die Aufgabe des Experimentes stets einen wichtigen Einfluß haben auf die Wahl des Versuchstieres, und wo das lebende Material reichlich zur Verfügung stehen muß, sind die Marine-laboratorien (sogenannte Biologische Stationen) den Binnenlands-laboratorien vorzuziehen. Erstens ist es ein fundamentales biologisches Prinzip, die wichtigeren Probleme, wenn möglich, immer zuerst an den einfacheren, mehr elementaren Lebewesen zu erforschen. Zweitens sind warmblütige Versuchstiere schwieriger zu erhalten und teurer als Seetiere, und drittens erfordert der Warmblüter einen komplizierteren Apparat zur Erhaltung physiologischer Bedingungen.

In jedem Biologic Laboratory des Bureau of Fisheries, wo dieselben an den langen Küsten der Vereinigten Staaten auch gelegen sein mögen, wird das lebende Versuchsmaterial und alle nötigen Reagenten und Apparate unentgeltlich geliefert.

Unter den Fischen, die am häufigsten vorkommen und daher stets reichlich in den Aquarien gehalten werden, befindet sich der von Mitchill *Cynais canis* und später von Spencer F. Baird *Mustelus canis* benannte Elasmobranchier, welche dem europäischen *Scyllium* annähernd entspricht; dieses Tier wird von den hiesigen Fischern „Dogfish“, d. h. Hundefisch, genannt. Diesem sehr ähnlich ist *Squalus acanthias* (Spiny dog fish). Der am häufigsten vorkommende Hai ist der *Carcharias littoralis* (Sandshark).

Die Technik, welche ich im nachfolgenden beschreiben werde, ist auf alle diese Elasmobranchier und ebenfalls auf Scyllium anwendbar, und ist deshalb hier veröffentlicht, weil ich in der einschlägigen Literatur weder Anweisungen über die Freilegung des Herzzweiges des Vagus vorfand, noch über die praktischste Art, das Herz für physiologische Untersuchungen zu präparieren.

### Die Narkose.

Für die meisten physiologischen Fragestellungen ist die Narkose unumgänglich. Bedauernswert ist es, daß man auf biologischen Stationen immer noch Arbeiter findet, die willens sind, solch ein edles Versuchstier ohne Narkose zu verstümmeln — denn Operieren kann man diese Tortur eines sich im Schmerz windenden Tieres nicht nennen. Feinere technische Eingriffe sind bei einem zuckenden Fisch ganz unausführbar.

Die Technik der Fischnarkose ist im ersten Band dieser Zeitschrift, S. 377, von Dr. A. Sulima sehr ausführlich beschrieben, und ich kann nur bestätigen, daß das Chloretone, welches dieser Verfasser Azetonchloroform nennt, allen anderen Anästhetizis bei weitem überlegen ist. Es ist das eigentlich kein Derivat des Chloroforms, sondern ein Alkohol, nämlich Trichlortertiärbutylalkohol, und zuerst von Randolph<sup>1)</sup> empfohlen.

Es ist zuweilen möglich, den Fisch ganz ohne chemische Mittel bewußtlos zu machen, nämlich durch Hypnose<sup>2)</sup>. Es gelang mir in der Hälfte aller Versuche, eine genügend tiefe Hypnose für die Operation zu erzeugen. Es gibt zwei Methoden, dies zustande zu bringen: 1. durch rhythmischen Druck über das Gehirn mit beiden Daumen ausgeübt, während das Tier in Meerwasser liegt, gerade tief genug, um die Kiemen zu bedecken. Ist es nach 5—10 Minuten anscheinend ruhig, so läßt man es sachte in ein tieferes Gefäß versinken; ist das Tier wirklich hypnotisiert, so sinkt es bewegungslos zu Boden, rollt zuweilen auf den Rücken und zeigt den weißlichen Bauch nach oben. Dann kann man das Tier behutsam herausnehmen und auf den Operationshalter binden. Die Zahl der Pressungen auf das Gehirn kann ca. 30 in der Minute betragen und zwar dürfen sie durchaus nicht kräftig ausgeführt werden.

Die zweite Methode besteht darin, daß man den Fisch mit

<sup>1)</sup> Zool. Anz., Bd. 23.

<sup>2)</sup> Siehe Verworn, Allgemeine Physiologie, über Hypnose von Schlangen, Hühnern, Krebsen usw.

beiden Händen fest packt und seinen Kopf unter einen sanften Strahl Meerwasser hält. Das Wasser darf nicht höher als 1—2 Fuß hoch fallen, und die Kiemen müssen unter Wasser bleiben. Nach 5—10 Minuten, wenn die Prozedur erfolgreich ist, reagiert das Tier wie bei der Gehirndruckhypnose. Warum die Tiere nicht immer hypnotisiert werden können, und ob dies wirklich Hypnose ist oder eine andere Art Betäubung, läßt sich gegenwärtig nicht beantworten. Sicher ist nur, daß, wenn die Hypnose gelingt, man die schönsten operativen und physiologischen Resultate erzielen kann. An Elasmobranchiern, die nur auf diese Art hypnotisiert waren, ist es mir gelungen, den Atmungs- und Herzrhythmus zu gleicher Zeit auf dem Kymographen zu registrieren, durch den Korakoidknorpel in das Perikardium zu bohren, eine Kanüle einzuführen und nach Unterbinden des Pleuroperitonealkanals den Perikardialdruck zu messen.

Bei den ersten Versuchen bezweifelten wir, ob der Fisch gesund war; so ruhig verhielt er sich, daß wir vermeinten, das Tier sei sonst am Zentralnervensystem beschädigt. Über diesen Zweifel wurden wir erhoben durch die Erfahrung, daß etliche dieser Canais noch zehn und zwölf Tage nach diesen Operationen im Aquarium lebten.

Für längere Operationen und Untersuchungen ist die Hypnose jedoch nicht zuverlässig und die Chloretonenarkose das ratsamste.

#### Lage und Haltung des Fisches auf dem Operationstisch.

In dem Handbuch der physiologischen Methodik, herausgegeben von Rob. Tigerstedt, fand ich weder eine Anweisung über die Befestigungsweise der Fische, noch über ihre spezielle Narkose, d. h. soweit dieses großartige Werk bis jetzt erschienen ist. Im ersten Band, Allgemeinen Methodik (S. 1—64), wird zwar dies Thema von einem Meister der Vivisektionstechnik behandelt — J. Pawlow —, doch findet sich nichts über die Fische, die das Hauptmaterial der biologischen Stationen liefern. Diese Technik läßt sich kurz fassen. Man darf den Fisch nicht durch ein Seil oder Riemen über die Kiemen noch über die Geschlechtsteile festbinden. Eine Schnur über Maul und Kiemen macht das Atmen unmöglich und komprimiert die großen Venen des Kopfes. An der Kloake der Elasmobranchier befinden sich die Ausgänge nicht nur der Geschlechtsapparate, Harnorgane und Magendarmkanals, sondern auch



die Mündungen zweier Kanäle, die den ganzen Peritonealraum drainieren. Da der Peritonealraum dieser Tiere direkt mit dem Perikardium in Verbindung steht, durch den sogenannten Pleuroperitonealkanal, kann eine Kompression über der Kloake schlimme Stauungen nicht allein aller Bauchorgane, sondern sogar des Perikardiums herbeiführen, speziell wenn sich die feste Ligatur lange genug an dieser Stelle befindet. Daher gibt es nur zwei Stellen, wo man diese Tiere folgenlos befestigen kann, 1. ganz vorne an der Schnauze, 2. kaudal von der Geschlechtsöffnung. Es ist daher eine tiefe Narkose erforderlich. Windet sich das Tier dennoch, so läßt man es am besten durch die Hand eines Assistenten halten, oder legt eine handbreite Bandage um die vorderen Flossen herum. Unter gewissen Bedingungen ist es vorteilhaft, das ganze Tier in Gaze einzuwickeln und auf beiden Seiten diese Gaze mit Stiften festzunageln. Man operiert dann durch diese Einhüllung hindurch. Bei genügender Narkose habe ich die vordere und hintere Befestigung für genügend befunden. Die Narkose, wie Dr. Sulima sie beschreibt (l. c.), kann bei großen Haifischen nicht angewandt werden, weil man dazu zu viel Chloretone anwenden müßte. Diese großen Tiere werden am besten in große Eisenblechkannen mit dem Kopf nach unten eingestülpt. Dann wird genügend  $\frac{1}{10}$  % ige Chloretonelösung zugegossen, bis alle Kiemen zugedeckt sind. Eine 2 % ige Lösung von Äther ist bei großen Haien ebenso effektiv und billiger. Leider kommt bei dieser Stellung eine Komplikation hinzu, die für die nachfolgende Operation gefährlich wird. Der Fisch steht auf dem Kopf und daher sammelt sich das Blut im Gehirn und um die Kiemen an, und es können sogar Stauungen im Sinus venosus-Gebiet vorkommen. Da die Atmung oft sistiert, fehlen die muskulösen Kontraktionen, die das oxygenierte Kiemenblut zurück durch die Dorsalaorta nach dem Herzen schicken. Operiert man nun, so ereignen sich Blutungen viel leichter, als bei einem normalen Fisch, da alle Gefäße von Blut strotzen. Da man nicht ohne große Ausgaben ein ganzes Aquarium voll der Chloretonelösung verwenden kann, und große Tiere sehr leicht bei einfacher Submersion des Kopfes narkotisiert werden können, lohnt es sich, vor Beginn der Operation den Kopf des Tieres einige Minuten hochzuhalten. Ist der Zweck der Operation in kurzer Zeit zu erreichen, so genügt es, einen Holzblock unter das Kopfbende des Fischhalters zu legen und die Kiemenatmung durch Einführung eines Schlauches in den Rachen fortzusetzen. Das einlaufende Wasser kann in kritischen Momenten abgedreht werden, z. B. wenn



es gilt den Vagus zu unterbinden. Es scheint mir, daß zuweilen Luft in die Kopfvenen absorbiert wird, wenn die Kiemen lange nicht unter Wasser sind. Doch ist das täuschend, da die Luft auch durch kleinste Venenläsionen eindringen kann.

### Präparierung des Ramus cardiacus vagi.

Um erfolgreich am Vagus zu operieren, muß man vorerst eine genaue anatomische Kenntnis seiner Verteilung und topographischen Beziehungen zu den anderen Kopfnerven und den großen Blutgefäßen besitzen. Diese Technik setzt eine solche Kenntnis voraus: (Refer. Gegenbauer, Vergl. Anat.; Wiedersheim, Vergl. Anat.); auch C. Judsons Herrick Monographie, *The Cranial and first Spinal Nerves of the Menidia* (Arch. of Neurol. and Psychopath., Bd. 2, 1899), enthält wertvolle Belehrung über dieses Thema. An den schönen Tafeln dieser letzten Arbeit läßt sich sofort erkennen, daß der Vagus unter der Laterallinie über die Kiemen herzieht und an jede Kieme einen vorderen und einen hinteren Ast abgibt (Anterior and posterior trematic branch of Vagus). Nach Abgabe dieser Kiemenäste verteilt sich der übrige Vagus auf Herz und Verdauungsorgane. Der Ramus cardiacus der Elasmobranchier verläuft dicht hinter der oberen Kante des fünften Kiemenbogens; dies ist der letzte Knorpelbogen vor dem Schulter-(Pektoral-)Gürtel. Bei Experimenten an diesem Herzzweig mit darauffolgender kymographischer Registrierung der chronotropischen und inotropischen Effekte des Vagus kommt es nicht nur darauf an, daß man den Ramus cardiacus freilegt und zwecks elektrischer Reizung unterbindet, sondern speziell, daß man ihn so blutlos wie möglich isoliert. Von geringer Kapillarblutung abgesehen, ist es mit einiger Sorgfalt möglich, diesen Herzzast blutlos zu unterbinden. Schwere Blutungen machen nicht nur genaue Blutdruckexperimente unmöglich, sondern sie verhüllen auch das Operationsfeld in Blut, welches, namentlich wenn es gerinnt, eine richtige Orientierung sehr schwierig macht.

Die Schwierigkeiten der blutlosen Freilegung des Ramus cardiacus werden dadurch vermehrt, daß dieser Vaguszweig hinter der Oberkante des fünften Kiemenbogens im Boden eines Venenblutsinus herläuft. Bei den ersten Versuchen möchte man fast annehmen, daß er frei im Grunde dieses Sinus liegt, der dem oberen Rand des fünften Kiemenbogens parallel verläuft, ja diesen Bogen fast umgreift. Weiterhin, nach dem Perikardium zu, tritt der Ramus cardiacus durch ein Foramen, durch welches er direkt

in die Wand des Sinus venosus des Herzens eintritt. Dasselbe Foramen ist aber auch der Anfang des Sinus von Cuvier, und ist von einem Venenblutsinus erfüllt. Eine Eröffnung des Sinus um den fünften Kiemenbogen oder des besprochenen Foramens zieht bedeutenden Blutverlust nach sich und führt auch zur Luftembolie des Vorhofs und Ventrikels. Registriert man nur mittels eines Hebels, der mit einem Faden an dem Ventrikel befestigt ist, so kann das Experiment immer noch teilweise erfolgreich sein. Registriert man aber mittels Quecksilbermanometer direkt von der Aorta aus, so machen Blutverlust und Luftembolie eine Fortsetzung des Versuchs nutzlos. Es kommt also darauf an, möglichst blutlos zu arbeiten. Bei der folgenden Beschreibung bitte ich die Zeichnungen zu studieren.

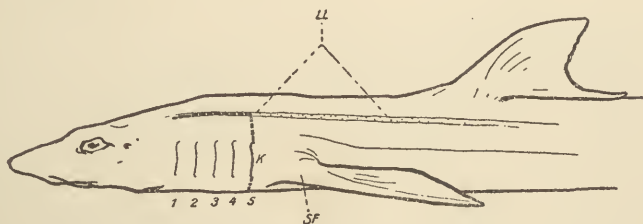


Fig 1.

#### Freilegung des Ramus cardiacus vagi am Selachier.

Erster Einschnitt K (5) = fünfte Kiemenöffnung, durch welche die Schere eingeführt wird. Dann folgt ein Schnitt nach dem Rückgrat zu bis zur lateralen Linie LL. Hierauf wird links nach dem Auge zu in der Linie LL aufgeschnitten bis zum ersten Kiemenschlitz (1). Dann setzt man die Schere in dem unteren Rand des fünften Kiemenschlitzes an und schneidet dicht an der Schulterflosse SF, hart am Schultergürtel entlang, bis ungefähr 6—8 cm von der unteren Mittellinie der Brust. Dabei große Sorgfalt, daß die fünfte Kieme nicht verletzt wird, für nachfolgende Schnitte siehe Figur 2.

Der erste Einschnitt wird von der letzten, d. h. fünften Kiemenöffnung aus gemacht (s. Fig. 1). Man benutzt dazu eine starke Schere, die abgerundete Klingen hat. Scheren mit spitzen Klingen können trotz Sorgfalt viel Unheil anrichten; indem sich das Tier bei geringster Bewegung die Klinge tiefer einstößt, als der Operateur beabsichtigt. Eine Klinge wird in die fünfte Kiemenöffnung eingeführt, dann erweitert man dieses Loch mit kräftigem Schnitt nach oben bis an die Laterallinie. Der Fisch liegt auf der rechten Seite und die linke weist nach oben. An der Laterallinie angekommen, führt man die Schere dicht unter der Haut her nach vorne, dem Auge zu, bis zur zweiten Kiemenöffnung, aber immer in der Seitenlinie bleibend, die leicht zu erkennen ist. Ist man so

weit, dann faßt man die Ecke dieses Lappens mit gezahnter, derber Pinzette in der linken Hand, mit der Schere in der rechten versucht man jetzt sorgfältig die Haut und subkutane Faszie von den unterliegenden Muskeln zu trennen. Es ist das ein nötiger Schritt, um den fünften Kiemenbogen und umliegendes Gewebe aufzudecken. Die Schnitte werden ganz oberflächlich geführt; tiefe Schnitte können leicht in den vorderen Kardinalsinus einreißen. Bei Führung der Schnitte dicht unter der Haut stößt man auf keine bedeutenden Gefäße. Diese liegen unter den Rückenmuskeln und mehr gegen die Mitte von der Laterallinie.

Ist man ohne Blutung so weit, daß die roten Falten der fünften Kieme freiliegen, so läßt man den oberen Teil des Lappens gehen und setzt die Schere in den unteren Rand desselben Kiemenlochs, den man vorhin nach oben zu aufschnitt. Nun schneidet man nach unten auf, dicht am Pektorgürtel vorbei, um die Seite des Fisches herum und in die Brustseite hinein. Dadurch bekommt man einen großen Lappen, der oben von der Laterallinie am Schultergürtel vorbei bis beinahe zur Mitte der Brustlinie reicht.

In diesem Stadium untersucht man alle leicht blutenden Punkte und unterbindet überall wo bedeutendere Blutung ist. Dies ist selten nötig, wenn man nicht direkt in die fünfte Kieme eingeschnitten hat oder den oberen Laterallinienschnitt zu tief gemacht hat. Denn fast alles Blut verläuft hier in der ventralen und dorsalen Aorta, die in der Mitte liegen. Man kann den Canais hier fast blutlos köpfen, wenn man diese beiden Hauptgefäße, die Kieme und die vorderen Kardinalsinus, nicht verletzt oder vorher doppelt unterbindet.

Der Lappen wird nun nach vorn übergelegt, wobei die fünfte Kieme mitgezogen wird; man sieht dann den fünften Kiemenbogen frei und unter diesem die Öffnung im Pharynx (vgl. Fig. 2). Bei *Scyllium canicula* oder *Catulus* und *Canais* von 2—3 kg kann man den Zeigefinger unter diesem Bogen in den Pharynx einführen und dadurch diesen Kiemenbogen während der weiteren Präparierung des *Ramus cardiacus* ruhig halten. Hinter dem oberen Rand dieses Knorpels läuft der Herzzweig, und ihm ist nur auf einer Strecke von höchstens 2 cm beizukommen, ehe er in das besprochene Foramen verschwindet.

Hat man sich durch vorherige Sektion mit den topographischen Verhältnissen vertraut gemacht, so weiß man, daß jetzt der schwierigste Schritt kommt, wenn man keine Blutung haben will. Das erzielt man auf zweierlei Art. Erstens kann man durch den fünften Kiemenbogen bohren, gerade auf den Nerven, und eine kleine



Stelle freilegen, die genügt, die Spitzen der Elektrode anzulegen. Das gelingt mit einiger Übung. Man sieht dann nur einen halben Zentimeter vom Ramus cardiacus, der unter der Reizung zuweilen ermüdet, da man keinen Raum zur Abwechslung hat. Zweitens unterbindet man den Sinus zusammen mit dem fünften Kiemenbogen am vorderen Ende, selbst auf die Gefahr hin, den Ramus cardiacus mit in die Schlinge zu fassen. Man kann dann später distal von der komprimierten Stelle reizen. Dann führt man mit scharfem Messer einen Schnitt parallel mit dem unteren Rand des fünften Kiemenbogens, hebt den Rand des Schnittes mit dem Griff des Messers, schält und schiebt ihn nach oben (man kann hier nicht schneiden, nur abschaben und zwar höchst behutsam). Mit einiger

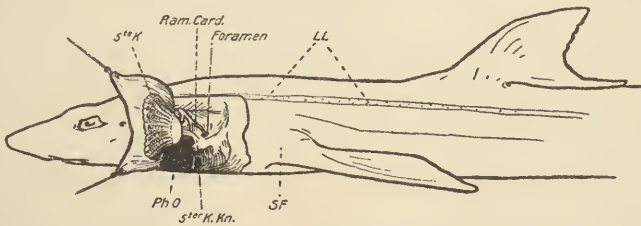


Fig. 2.

Freilegung des Ramus cardiacus vagi am Elasmobranchier (Canais, Mustelus canis, Scyllium usw.).

Zweiter Teil der Operation. Zurücksektierung des Hautlappens samt der fünften Kieme (5te K); Ram. Card. = Herzzast des Vagus; Foramen = durch welches er in den Sinus venosus eintritt; LL = Laterallinie; SF = Schulterflosse; 5ter K. Kn. = fünfter Kiemenknorpel; Ph O = Pharynxöffnung. Der Venensinus, unter welchem der Ramus cardiacus vagi, kann in einer schematischen Zeichnung nicht wiedergegeben werden. Der fünfte Kiemenbogenknorpel ist auch schematisch und herabgedrückt. Durch das Pharynxloch (Ph O) wird der kleine, oder bei großen Exemplaren der Zeigefinger der linken Hand eingeführt und damit der fünfte Kiemenbogen zart emporgehoben und in konstanter Lage gehalten, während mit der rechten Hand der Kiemenbogensinus sachte zurückgeschoben wird.

Geduld wird der Herzzweig erkennbar, wie er als weiße Linie hinter diesem Bogen zum Foramen läuft. Immer noch mit dem kleinen oder Zeigefinger der linken Hand unter dem fünften Kiemenbogen diesen fixierend, führt man an beiden Seiten des Ramus cardiacus zwei leichte Schnitte, um ihn von der umgebenden Faszie zu befreien, hebt ihn mit untergeschobenem Haken ab, führt die Ligatur unter ihm durch, zieht den Finger aus dem Pharynx und läßt das Operationsfeld im „Statu quo ante“ versinken. Darauf nachträgliche Unterbindung aller blutenden Stellen; wo Unterbindung unmöglich ist, wird mit feiner Zange die blutende Stelle entweder zugeedrückt, gepreßt oder abgedreht.



Bei allen Unterbindungen von Gefäßen oder Nerven ist es zu beherzigen, daß sich die Ligaturen und Fäden sehr leicht an der äußeren Haut dieser Fische fangen, und zwar so fest, daß man meint, der Faden hänge an einem Haken, weil eben die Haut der Elasmobranchier von kleinen harten Erhebungen so dicht besät ist, daß sie sich wie Sandpapier anfühlt, alle Messer und Scheren rasch abstumpft und die Ligaturen regelmäßig fängt. Eignet sich solch ein Haftenbleiben der Fäden, z. B. beim Unterbinden des Vagus oder der Aorta, so hüte man sich an dem Faden zu ziehen; er kommt dann in der Regel mit einem plötzlichen Ruck los und reißt den Nerven oder das Gefäß ab. Wenn ein untergeschobener Faden nicht sofort glatt durchgeht, so hebe man ihn sorgfältig von der nassen Haut ab und halte ihn beim Durchziehen und Binden frei in der Luft; ist er lose um das Gefäß usw. gelegt, so schneide man alle unnötigen Fäden so kurz wie möglich ab. Sind irgendwo längere nötig, so lege man sie zusammengerollt in die Wunde, nicht auf die Haut.

#### Fischhalter und das Festbinden des Tieres.

Es kommt darauf an, was man bezwecken will, welches Gefäß, welchen Nerven oder welches Organ man freilegen will. Danach muß sich die Konstruktion des Halters richten. Auch ist es fast immer vorzuziehen, daß der Fisch normal atmet, oder mindestens, daß die Kiemen während der Operation unter Seewasser gehalten werden. Dies kann auf irgend einem Halter erreicht werden, indem ein Schlauch im Maul befestigt wird, der mit einem Reservoir, mit Seewasser angefüllt, in Verbindung steht. In Marinelaboratorien ist auch das Reservoir in der Regel entbehrlich, weil fast in allen Sälen und Zimmern das Seewasser aus Röhren unter gelindem Druck zu erhalten ist. Ein solcher, im Rachen festgebundener Schlauch ist bei der Vaguspräparierung dem gänzlichen Eintauchen des Kopfes vorzuziehen, eben darum, weil man am Kopf operieren muß, der erste Einschnitt geschieht durch die fünfte Kiemenöffnung. Die Stellung, welche Dr. Sulima<sup>1)</sup> vorschlägt, ist für Operationen an den Verdauungs-, Harn- und Geschlechtsorganen zu empfehlen, weil man diese Partien leicht vor Eindringen des Meerwassers schützen kann. Will man aber physikalisch-chemische Studien am Herzen oder den großen Gefäßen machen, so ist das konstante Eindringen von Meerwasser durchaus nicht eine gleichgültige Sache, wie es von manchen Arbeitern hingestellt wird. Zum Zweck der

<sup>1)</sup> Diese Zeitschrift, Bd. 1, S. 381.

Reizung irgend eines Teiles des Herzens ist es vorzuziehen, daß die Perikardialhöhle so rein wie möglich von Meerwasser und Blut gehalten wird. Denn diese Lösungen enthalten Elektrolyten, deren Ionen den Strom rasch über das ganze Herz verbreiten; man kann danach kaum einen spezifischen Teil allein stimulieren. Der empfindlichste Teil ist der Sinus venosus, und auf diesem speziell der Punkt, wo die Akzeleratoren sich verknoten. (Ich rede wohlbedacht von Kreuzung oder oberflächlichem Verlaufen von Akzeleratorenfaser, nicht von Ganglien, weil ich noch nicht überzeugt bin, ob dieser Beschleunigungspunkt am Sinus von Raia, Canais und Carcharias, den ich diesen Sommer fand, Ganglienzellen enthält; die weiteren mikroskopischen Studien werden das feststellen.) Jedenfalls ist dies die empfindlichste Stelle am ganzen Herzen, daher erkläre ich mir das Resultat, daß man bei nicht sorgfältiger Reizung meistens Beschleunigung des Herzrhythmus erhält, weil eben die Lösung, welche das Perikardium anfüllt, den Strom verteilt und stets der empfindlichste Punkt am kräftigsten reagiert. Ist aber die Perikardialhöhle ziemlich trocken, so kann man den Inhibitions-(chronotropisch-dromotropisch negativen) Punkt einzeln reizen und beliebig durch abwechselnde Stimulierung des Akzeleratoren- oder Inhibitionspunktes Beschleunigung oder Stillstand hervorrufen. Es ist also wichtig, den Perikardialraum von Meerwasser und Gerinnseln rein zu halten. Ein besonders beliebter Fischhalter bei meinen Arbeiten enthielt in einem Meter langen und einem viertel Meter breiten Holztrog einen Holzschemel, mit flacher Seite nach unten und den ausgesägten Füßen nach oben, ungefähr in dieser Figur.



Der Schemel war im ganzen Halter verschiebbar und diente zum Erheben und Ruhighalten des gerade zu operierenden Abschnittes. Der Trog war innen mit Zink belegt und konnte mit Seewasser gefüllt werden, so daß im Notfalle der Kopf zu jeder Zeit eingetaucht werden konnte.

Freilegung und Isolierung des Herzens von Canais-  
*Mustelus canis*, *Scyllium* und *Carcharias littoralis*.

Die Technik der Exponierung des Herzens bei diesen Fischen bietet keine besonderen Schwierigkeiten, wenn man bei dem Durchschneiden des Korakoidknorpels (sog. Brustknorpel) Vorsicht übt.

Zwei weitere Vorsichtsmaßnahmen sind: a) doppelte Unterbindung der Gefäße unter den Korakobranchial- und Korakomandibularmuskeln; b) das Herz selbst so wenig wie möglich zu berühren. Die äußere Haut wird in der Mitte des Korakoidknorpels derb mit der gezahnten Pinzette erfaßt und mit der linken Hand emporgezogen; mit der scharf geschliffenen, jedoch stumpfendigen Schere in der rechten wird ein Loch in das hochgezogene Hautstück geschnitten. In dies Loch wird eine Klinge der Schere eingeführt und damit die Öffnung nach dem Unterkiefer zu erweitert, bis etwa 2 cm vom Unterkieferknorpel. Zunächst führt man die Schere in das kaudale Ende des Schnittes und erweitert diesen über das Korakoid hinweg ca. 5 cm nach dem Abdomen zu.

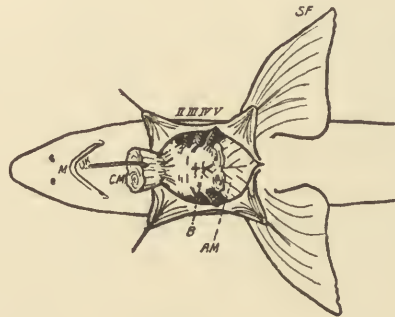


Fig. 3.

Freilegung des Herzens der Selachier. (Illustriert bei *Scyllium* und *Mustelus canis*.)

II III IV V = 2.—5. Kieme; M = Maul; UK = Unterkiefer; CM = Coracomandibularmuskel, zusammen mit Coracohyoidmuskel; B = Blutgefäße zwischen Coracomandibular- und Coracobranchialmuskelschicht; AM = Muskel des oberen Abdomens; SF = Schulterflosse.

In der Linie zwischen den beiden Schulterflossen wird nun die Haut von der Mitte nach rechts und links durchschnitten, bis um den Ansatz dieser Flossen herum. Die ganze Hautöffnung klafft jetzt in Form eines Kreuzes auseinander, und wenn die Ecken der Epidermis fest gefaßt werden, kann sie leicht wie beim Frosch abgezogen werden, nur daß es beim Hai mehr Kraft bedarf.

Die Hals- und Brustmuskeln liegen jetzt bloß, und es gilt zunächst die Muskeln zwischen dem oberen Rand des Korakoids und dem Hyoid, dem Kiefer und Kiemenknorpeln nach oben hinwegzupräparieren, oben abzubinden und abzuschneiden; dann erst erscheint die weißliche Kapsel des Perikardiums. Die Muskeln, welche von dem einem Korakoid entsprechenden Teile des Schultergürtels aus-



gehen, sind<sup>1)</sup> 1. Coraco branchialis vom Korakoid nach den Kiemen, 2. Coraco hyoideus vom Korakoid nach dem Hyoidknorpel, 3. Coraco mandibularis vom Korakoid nach dem Unterkiefer.

Beim Ansatz von Nr. 1, dicht am Korakoidknorpel, wird ein tiefer Einschnitt rechts und links gemacht, der Rand des Schnittes mit gezahnter Pinzette gefaßt und mittels Messer oder Schere nach dem Kiefer zu abgelöst. Desgleichen Nr. 2 und 3. Flach zwischen 2 und 3 laufen die äußeren Halsgefäße, zwei an der Zahl, die stark bluten und nachher das geöffnete Perikardium mit Gerinnseln anfüllen. Sie müssen daher doppelt unterbunden werden, ehe man sie durchschneidet. Überhaupt ist hier alle Blutung zu stillen, wenn man später ein blutfreies Perikardium haben will. Blutung ver-

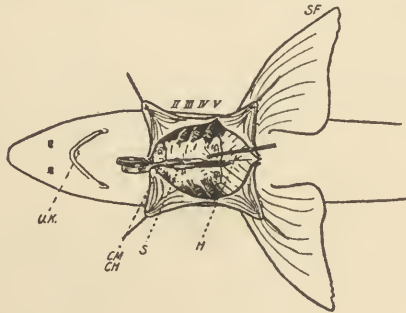


Fig. 4.

Freilegung des Herzens des Selachier.

II III IV V = 2.—5. Kieme; UK = Unterkiefer; CM und CH = Stumpf der abgeschnittenen Coracomandibular- und Hyoidmuskeln; SF = Schulterflosse; S = Schere, unter dem Korakoidknorpel in das Perikardium eingeführt, während dieser Brustknorpel mit dem H = Haken emporgezogen wird, um bei Durchtrennung der Mitte des Knorpels eine Verwundung des Herzens zu vermeiden.

hindert genaue Orientierung im Operationsfeld, erniedrigt den Blutdruck und beeinträchtigt die Arbeit des Herzens mechanisch, indem geronnenes Blut den Vorhof und Ventrikel in ihren Kontraktionen hindert. Sind die eben erwähnten drei Muskelschichten abgetrennt (man kann sie auch „in toto“ abtrennen), so werden sie mit einem starken Faden umschnürt und ungefähr 2—3 cm diesseits des Unterkiefers abgeschnitten und entfernt. Die flachen Brustmuskeln werden dann ebenfalls präpariert und auf 3—4 cm nach dem Abdomen zu entfernt, um den Durchschnitt durch die Mitte des Korakoidknorpels zu erleichtern. Jetzt ergreift man mit feingezahnter Pinzette die zähe Faszie dicht oberhalb der Mitte des Korakoid-

<sup>1)</sup> Gegenbauer, Vergl. Anat., Bd. 1, S. 652.



knorpels, hebt sie ein wenig empor und schneidet vorsichtig ein kleines Loch hinein. Mit zwei Pinzetten hält man dieses auseinander und späht in das Perikardium hinein, um festzustellen, ob das Herz geschwollen ist und beinahe durch die Öffnung ragt oder auf den dorsalen Grund der Herzhöhle zurücksinkt. Ist das erstere der Fall, dann hebe man das Kopfende des Halters hoch, bis das Herz kleiner wird; bleibt es anscheinend geschwollen, dann ist die weitere Öffnung des Korakoidknorpels kritisch.

Um Verwundung des Herzens zu meiden, lasse man durch einen Assistenten einen Haken durch die Mitte oder unter das Korakoid führen und dieses emporziehen; dann erst führt man eine starke stumpfendige Schere unter die Mitte dieses Brustknorpels und trennt ihn durch. Darauf werden beide Brustknorpel rechts und links mit

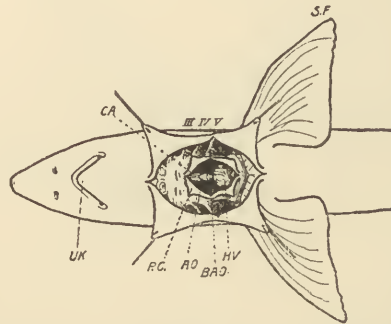


Fig. 5.

Freilegung des Selachierherzens.

III IV V = 3.—5. Kieme; UK = Unterkiefer; CA = Coronararterien; PC = Perikardium; AO = Aorta; BAO = Bulbus aortae; HV = Herzventrikel; CA = Coronararterien, von den Kiemen das Blut nach dem Herz zurückleitend; SF = Schulterflosse.

der Zange abgezwickelt, unter steter Beobachtung des Herzens, und zwar fast bis zum Ansatz der Schulterflosse. Hier ist Vorsicht geboten, denn wo dieser Knorpel unter die Schulterflosse hinunterzieht, biegt auch von unten und dem Abdomen her ein großer Venensinus ein, um sich kaudal vom Cuvierschen Sinus, unter und innen von der Schulterflosse, mit dem letzteren zu vereinigen. Man bleibe daher rechts und links 2 cm von dem Ansatz dieser Flosse. Ist die Entfernung der Mitte des Brustknorpels ohne Verwundung des Herzens gelungen, dann schneidet man das übrige Perikardium mit der Schere nach dem Kiefer zu auf, nur ganz kleine Schnitte auf einmal ausführend und bei jedem Schnitt nachsehend, wie weit der Herzbeutel sich noch erstreckt, ehe die Kiemenarterien abgegeben werden. Diese lassen sich leicht erkennen; sieht man die ersten,

so höre man mit der Erweiterung auf. Den Schluß dieser Operation bildet die lose Anlegung von Ligaturen zwecks späteren Einbindens von Kanülen in den Bulbus arteriosus und den Sinus venosus.

Spezielle Sorgfalt bedarf das Umlegen einer Ligatur um den Sinus venosus, da dieser höchst empfindliche Herzteil leicht dauernd geschädigt wird, ja schon bei geschicktester Unterziehung eines Fadens ändert sich der Rhythmus sofort. Auch ist es bei etwas erweiterten Vorhöfen fast unvermeidbar, einen Teil derselben mit in die Schlinge zu ziehen. Ein oft erfolgreicher „Trick“, dies zu vermeiden, besteht darin, daß man den Schwanzteil des Tieres erhebt, damit Aurikel und Ventrikel nach vorne fallen; dann führt man von links einen fadenlosen Haken unter den Sinus, hebt ihn sanft empor, worauf von rechts der mit Faden versehene Haken leicht durchgeführt wird. Die Herzen von Haifischen sind wohl leichter zu handhaben, und wegen der Größe ist Einführung von Kanülen leichter, doch sind sie nicht so resistent und sterben viel eher ab, als die Herzen von *Mustelus canis*, *Scyllium* und *Canais canis*.

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(Aus dem biologischen Marinelaboratorium des United States Bureau of Fisheries zu Woods Hole Mass.)

## **Methodik der gleichzeitigen Registrierung des Atmungs- und Herzrhythmus beim Selachier.**

Von

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Physiologische Untersuchungen über die Biophysik oder Mechanik der Atmung bei den Fischen in ihrer Beziehung zur Zirkulation sind noch sehr selten. Die Chemie der Respiration dieser Tiere ist in der bezüglichen Literatur schon reichlicher vertreten. Dennoch ist die Respirationsmechanik von fundamentaler Bedeutung für die vergleichende und allgemeine Physiologie des Herzens.

Da sind es besonders zwei Probleme, die noch der vollkommenen Lösung harren. Erstens: Welche Nerven beherrschen den muskulösen Teil des Respirationsapparates des Fisches? Spielt speziell der Vagus dabei eine Rolle? Zweitens: In welcher Weise beeinflussen die Atmungsphysik und der Wasserstrom die Arbeit des Herzens? Besonders die Technik der Lösung der zweiten Fragestellung soll uns hier interessieren. Das Perikardium der Haiarten, von den verschiedenen Typen von Scyllium, Mustelus und Raja, ist ein zäher, festgeschlossener birnenförmiger Sack, der das Herz — also Sinus venosus, Vorkammer und Ventrikel — den Bulbus arteriosus und den größeren Teil der kurzen, aber dickwandigen Aorta enthält. Sinus venosus und Vorkammer sind zarte, sehr elastische Gebilde und geben dem gelindesten Druck nach. Der Ventrikel ist ein starkes, muskulöses Bauwerk, welches, soweit ich diese Seite des Problems einer Untersuchung unterwerfen konnte, von den in diesem Perikardium möglichen Druckverhältnissen weder in positivem noch in negativem Sinne beeinflußt werden kann. Dies ist auch vom Bulbus arteriosus und der Aorta zu sagen. Einen Begriff von der Kraft des Ventrikels kann ich geben, indem ich den Druck, mit Quecksilbermanometer gemessen, welchen ich in der Aorta fand, hier mitteile. Bei drei kräftigen Exemplaren von

*Mustelus canis*, die respektive 16, 17 und 17 $\frac{1}{2}$  Pfund wogen, betrug der Durchschnittsdruck in der Ventralaorta 74 mm Quecksilber. Also die Frage verengt sich zu folgender Einsicht: Die Respirationsbewegungen können nur die Füllung des Vorhofs und des Sinus beeinflussen, denn Druckverhältnisse, die bedeutend genug wären den Ventrikel und die Aorta zu beeinflussen, kommen nicht vor. Die Fragestellung verengt sich noch mehr, speziell bei diesen Fischen, durch einen seltenen und höchst charakteristischen anatomischen Befund, den sogenannten Pleuroperitonealkanal der Selachier, wodurch das Perikardium dieser interessanten Tiere direkt mit dem Peritoneum in Verbindung steht. Und zwar ist das durchaus kein kleiner Verbindungsweg, sondern ein Duktus, der bei einem Scyllium von 3 kg einen gewöhnlichen Bleistift einführen läßt. Bedenkt man des weiteren, daß bei diesen Elasmobranchiern der Peritonealraum durch zwei Kanäle mit der Kloake in direkter Verbindung steht, so ist es ersichtlich, daß das Perikardium dieser Tiere durch Kanäle von zweierlei Art direkt mit der Außenwelt (dem Seewasser) kommuniziert. Doch ist das nur so möglich, daß zwar Flüssigkeit aus dem Perikardium in den Peritonealraum ablaufen kann, aber nicht umgekehrt. Klappen im Pleuroperitonealkanal verhindern das. Das Peritoneum wiederum kann leicht nach außen drainieren, aber das Seewasser kann nicht eindringen.

Die Fragestellung ist deswegen eingeengt, weil durch diese anatomische Besonderheit im Perikardium der Selachier ein positiver Druck unmöglich ist. Im Peritonealraum ist ebenso ein positiver Druck unmöglich, oder höchstens nur ein Druck solchen Grades, der genügt, die Resistenz der Klappen in diesen Kanälen zu überwinden.

Bindet man den Pleuroperitonealkanal dicht unter dem Cuvierschen Sinus im Abdomen des Hais oder *Mustelus* ab und näht die Bauchwunde genau wieder zu und bringt das Tier in ein großes Aquarium, so verhält es sich zuerst normal; binnen 3—5 Stunden zeigt es Symptome der Erstickung und ist gewöhnlich nach 16 Stunden tot. Daß die Operation an sich nicht daran schuld ist, beweist die Tatsache, daß solche Fische mit unterbundenem Pleuroperitonealkanal noch sechs Tage nach derselben Operation gelebt haben, wenn ich durch den Korakoidknorpel hindurch ein Loch in das Perikardium gebohrt hatte, wodurch die sich um das Herz ansammelnde Flüssigkeit nach außen abfließen konnte. Folglich erstickt der Fisch, weil sich das Herz wegen des ansammelnden Plasmas (?) nicht in Diastole ausdehnen kann. Diese Ansammlung



zu verhindern, das ist der Zweck des Perikardioperitonealkanal<sup>1)</sup>. Wollte man ausfindig machen, ob z. B. der Vagus im Sinne Lucianis<sup>2)</sup> der diastolische Herznerv sei, so ließe sich das beim Selachier nicht untersuchen, denn wegen des besprochenen Kanals läßt sich auch experimentell kein positiver Druck im Perikardium erzeugen. Führt man durch den Korakoidknorpel mittels Kanüle isotonische Salzlösung (20 g NaCl, 20 g Harnstoff, 1 l H<sub>2</sub>O) in das Perikardium ein, so läuft sie sofort in den Peritonealraum ab. Man ist dann gezwungen, die Verbindung dieser beiden Räume zu blockieren. Aber dies und den folgenden positiven Druck auf den Sinus und Vorhof verträgt das Tier nicht lange, jedoch lange genug zuweilen, um den Vagus zu reizen und die resultierenden Druckänderungen aufzuzeichnen.

Experimente, die auf die reziproke Beeinflussung von Respiration und Herzaktion zielen, müssen am völlig natürlichen Tier ausgeführt werden; so daß man selbst nicht die Chloretonnarkose anzuwenden braucht, denn meiner Erfahrung nach stört dies Narkotikum beide Funktionen. Man darf überhaupt nicht viel operieren. Die Atmung läßt sich ohne irgend welche Verletzung registrieren. Wenn nur der Rhythmus des Herzens beobachtet werden soll, so kann man diesen ebenfalls ohne gefährliche Eingriffe registrieren. Wenn die Atmungsbewegungen die Vorhofsystole unterstützen sollen, wäre das am ehesten zu bewirken, wenn beide synchron wären. Wenn nicht mit jeder Aurikularsystole, so vielleicht mit jeder zweiten oder dritten Systole müßte eine Atmung stattfinden. Die Begünstigung des Zuflusses von Blut von den Kiemen nach dem Sinus durch die Atembewegung geschieht dann möglicherweise noch durch Kompression der Venae cardinales anteriores (Jugularen), in denen ein Rückfluß vom Cuvierschen Sinus durch Klappen verhindert wird. Eine zweite Möglichkeit ist folgende: Die Muskeln, welche die Atmung bewirken (1. Korakomandibular-, 2. Korakobranchial-, Korakohyoidgruppe), laufen sämtlich über das Perikardium hinweg und könnten durch Zug auf dieses eine Vergrößerung und dadurch einen negativen Druck im Perikardialraum erzeugen. Diese Beziehungen lassen sich nur untersuchen durch gleichzeitige Registrierung des Atmungsrythmus, des Perikardialdruckes und des Herzrhythmus.

<sup>1)</sup> Pleuroperitonealkanal ist eigentlich eine unrichtige Bezeichnung, weil die Fische keinen Pleuralraum besitzen. Perikardioperitonealkanal ist richtiger.

<sup>2)</sup> Siehe Physiologie des Menschen, Bd. 1, S. 170.

Blutlose Methode, die Atmungsbewegung zu registrieren.

In einen dünnwandigen Gummiballon von länglicher (Zeigefinger-)Form wird eine lange Gummiröhre fest eingebunden. An der Stelle, wo diese Röhre einmündet und am entgegengesetzten Ende wird ein starker Seidenfaden fest eingebunden. An der Knorpelkante des Mauls wird eine Rinne eingekerbt und die Gummiröhre hier fest eingebunden. Den Gummiballon selbst führt man in den Rachen des Tieres ein und zieht den vorderen an der Röhre befestigten Faden durch das erste Kiemenloch, dann den am Ende des Gummiballons befestigten durch das fünfte Kiemenloch, und außerhalb der Kiemenlöcher bindet man beide Fäden leicht zusammen, so daß der im Rachen liegende Ballon nicht ausgespült werden kann. Man kann die Röhre durch ein Loch an den Kiemen der anderen Seite ausführen, anstatt aus dem Maul. Diese Röhre wird mit einer Mareyschen Kapsel verbunden, die mittels Schreibhebel am Kymographen registriert. Man erhält so sehr schöne Kurven. Alle Manipulationen werden unter Seewasser ausgeführt; nachdem die Fische sich selbst überlassen im Aquarium umherschwimmen, versöhnen sie sich rasch mit dem Apparat. Nur muß der Schlauch, welcher den Maulballon mit der Mareyschen Kapsel verbindet, lang genug sein, um Schwimmbewegungen zu ermöglichen. Gewöhnlich genügt dazu ein Meter. Zwischen dem Aquarium und dem Registrierapparat muß eine dünne Holzwand aufgestellt werden, um die Bespritzung mit Seewasser zu verhindern.

Versuche, die Fischatmung durch Fäden zu registrieren, die mit der Nadel direkt in einen oder den anderen Respirationsmuskel eingezogen sind, gelingen auch zuweilen. Doch ist es unmöglich, ohne Narkose einen solchen Faden mit Schreibhebel arbeiten zu lassen. Der Vorzug der Ballon-Mareykapsel-Methode besteht darin, daß der Fisch natürlich atmet und im Seewasser umherschwimmt.

Die Methode, den Herzrhythmus zu registrieren, ohne ein Manometer mit der Aorta zu verbinden und ohne Verletzung des Organs, besteht im folgenden. Wenn die Hypnose gelingt, ist diese vorzuziehen; sollte sie mißlingen, so wende man noch kein Chloretone oder Äther an, sondern nur lokale Anästhesie. Eine halbe Stunde vor dem Versuch wird über der Mitte des Korakoidknorpels eine 5% ige Kokainlösung unter die Haut gespritzt (3—4 Tropfen); oft genügt es, eine solche Lösung einzureiben, während dieser Teil über dem Wasser gehalten wird. Zwei Assi-

stenten halten das Tier, einer an der Schnauze, der zweite am Schwanze. Nun bohrt man langsam und vorsichtig eine 3—4 mm weite Öffnung mit dem Korkbohrer durch die Mitte des Korakoidknorpels. Es ist von Wert, an anderen Exemplaren die Dicke des Knorpels hier festgestellt zu haben. Man ziehe den Bohrer häufig heraus, um nachzusehen, wie weit man vorgedrungen ist, und hüte sich wohl, mit einem Ruck plötzlich in das Perikardium einzudringen. Ist das Loch gelungen, fügt man eine gut passende Kanüle ein und verbindet diese mit einem Wassermanometer. Positiven Druck bekommt man nicht, ohne vorher den Perikardioperitonealkanal abzuschließen, doch sind die Bewegungen im Wassermanometer deutlich genug, um registriert zu werden. Der Fisch wird, während Perikardialkanüle und Atmungsregistrierballon zu gleicher Zeit am Tier befestigt sind, im Aquarium belassen. Nach diesen Eingriffen erholen sie sich rasch; ich habe solche Tiere während einer ganzen Woche beobachtet.

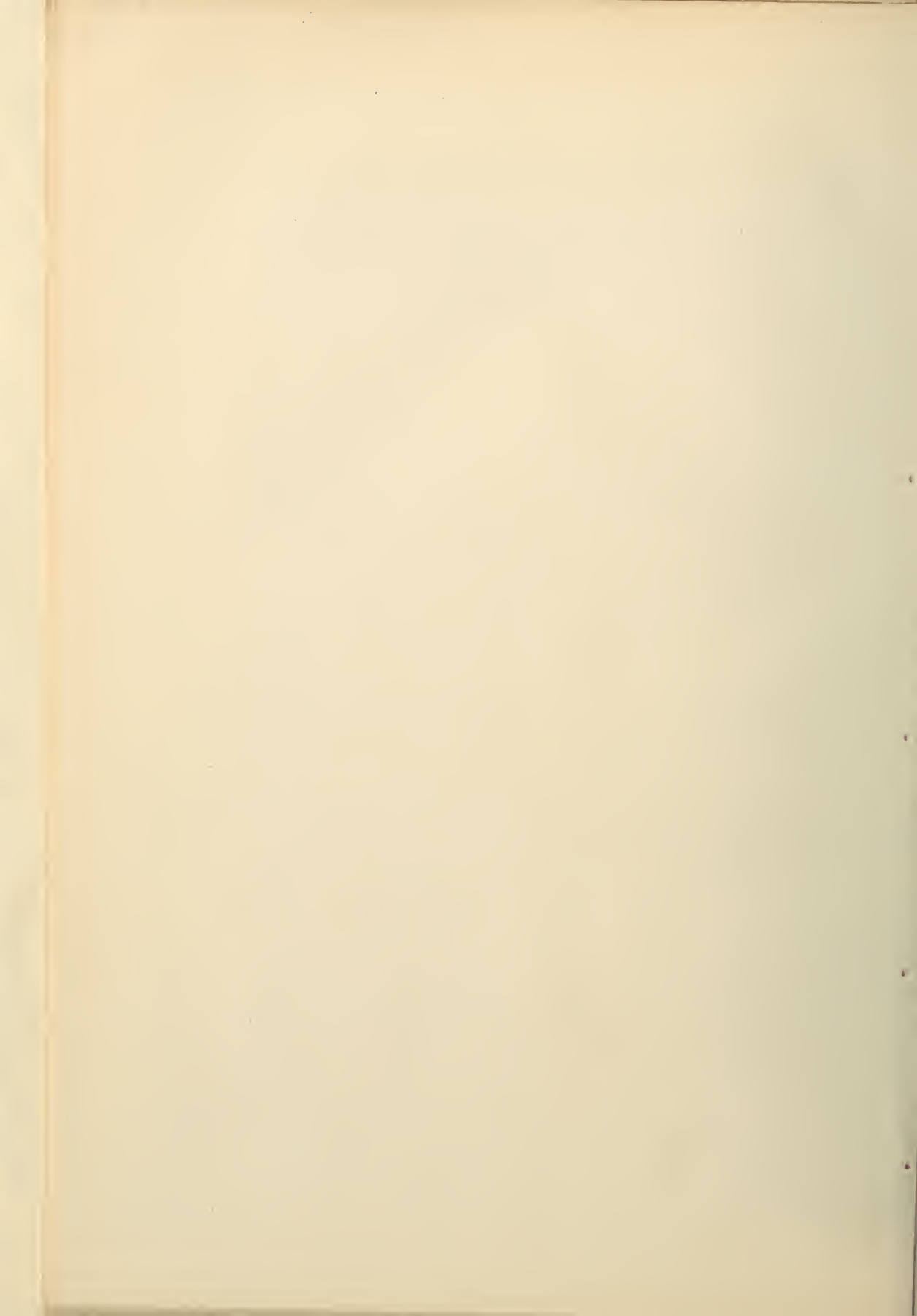
Es ist hier nicht die geeignete Stelle, von Resultaten der Methode zu sprechen, doch kann es nicht schaden, zu bemerken, daß Atmungsbewegungen und Herzrhythmus so selten synchron verlaufen, daß man dies beim Selachier wenigstens für zufällig ansehen kann. Der Zweck irgend einer Begünstigung der Herzfüllung durch Atmung besteht darin, den Cuvierschen Sinus wie ein Blutreservoir konstant voll zu halten und dadurch es dem Sinus venosus zu ermöglichen, sich selbst durch seinen reichlichen Nerven-, Muskel- und Klappenapparat nach Bedarf zu füllen. Daß dabei bestimmte Ganglienzellen am Sinus eine wichtige Rolle spielen, werde ich in einer weiteren Mitteilung darzulegen suchen.

Eine dritte Art, das Blut von den Kiemen nach dem Perikardium (Sinus venosus) zurückzubefördern, hat schon Frédéricq beschrieben; sie besteht in folgendem. Bei jeder Systole des Ventrikels und auch des Aurikels verkleinern sich diese bedeutend, auf diese Weise entsteht ein geringer negativer Druck im Perikardium, besonders wenn durch gleichzeitige Zusammenziehung der Respirationsmuskeln (*Coraco branchialis*) von außen her ein Zug auf das zähe Perikardium ausgeübt wird. Der dadurch entstandene negative Druck reicht aus, um den Sinus venosus vom Cuvierschen Sinus aus zu füllen. Der vorhin beschriebene Perikardioperitonealduktus kann einen positiven Druck verhindern, nicht aber einen negativen, weil Flüssigkeit aus dem Perikardium entweichen kann, jedoch nicht von der Peritonealseite aus eintreten kann. Die Erklärung Frédéricqs kann auf die oben gegebene Art erprobt werden, d. h.

gleichzeitige Registrierung der Atembewegungen und des Herzrhythmus mit Perikardialdruck. Seine Beobachtungen wurden nicht an Selachiern angestellt, sondern an Teleostiern, bei denen die erwähnte offene Verbindung des Perikardiums und Peritoneums fehlt und daher auch ein zeitweiliger positiver Druck im Perikardium denkbar wäre; der physiologische Zweck eines solchen Druckes, wenn er vorkommt, ist noch nicht erklärt.

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Der erste Band dieser Zeitschrift, der 1908/09 erschien (454 Seiten mit 161 Abbildungen im Text und einer Tafel, sowie Ergänzungsheft, 34 Seiten mit einem Plane und 20 Abbildungen, zusammen M. 17.80) enthält folgende Originalmitteilungen:

- J. Rich. Ewald** (Straßburg): Über Verwendung rotierender Spiegel zu physiologischen Untersuchungen. I. Das Zykloskop. Mit 3 Figuren.
- Dr. Wilhelm Berndt** (Berlin): Apparat zum Aufhängen und Aufbewahren von Wandtafeln. Mit 5 Figuren.
- Prof. T. Thunberg** (Lund): Über die Anwendung eines Platinbrenners zum Schreiben auf Glas und für ähnliche Zwecke. Mit 1 Figur.
- Prof. Wilhelm Roux** (Halle a. S.): Eine Methode der Selbstkopolation von Tropfen. Mit 1 Figur.
- H. Zwaardemaker** (Utrecht): Die Herstellung von Mischgerüchen. Mit 2 Figuren.
- O. Langendorff** (Rostock): Ein Versuch zur allgemeinen Muskelphysiologie. Mit 2 Figuren.
- J. K. A. Wertheim-Salomonsen** (Amsterdam): Anfertigung und Gebrauch dünner versilberter Quarzfäden. Mit 6 Figuren.
- F. Mandel**: Ein neuer Apparat zur Durchblutung überlebender Organe. Mit 1 Figur.
- Martin Gildemeister** (Straßburg): Ein Vogelmuskel, der sich besonders gut zu physiologischen Versuchen eignet. Mit 1 Figur.
- Otto Weiß** (Königsberg i. Pr.): Die Seifenlamelle als schallregistrierende Membran im Phonoskop. Mit 3 Figuren.
- Dr. Gerhard Joachim** (Königsberg i. Pr.): Über die Anwendung der Weißschen Registriermethode in der Klinik.
- Erich Herrmann** (Königsberg i. Pr.): Registrierung von Streichinstrumentklängen mit dem Phonoskop.
- N. E. Wedensky** (St. Petersburg): Ein neuer Induktionsapparat für Reizung mit ausgeglichenen und nicht ausgeglichenen Induktionsströmungen. Mit 2 Figuren.
- Otto Frank** (Gießen): Ein Kymographium für photographische Registrierung. Mit 2 Figuren.
- Dr. J. Seemann** (Gießen): Neue Aufnahmen der menschlichen Stimme. Mit 5 Figuren.
- Otto Weiß** (Königsberg i. Pr.): Zwei Apparate zur Reproduktion von Herztönen und Herzgeräuschen. Mit 3 Figuren.
- Albrecht Bethe** (Straßburg): Ein handlicher Apparat zur mechanischen Reizung. Mit 2 Figuren.
- Die Verwendung des Solenoids zum langsamen Aufsetzen und Abheben von Gewichten, oder zur Veränderung ihres Druckes gegen die Unterlage. Mit 1 Figur.
- Edgard Zuaz** (Brüssel): Eine Kanüle zur Cholechoenterostomie. Mit 1 Figur.
- R. Burlan** (Neapel): Methodische Bemerkungen über Nervmuskelpreparate von Oktopoden. Mit 5 Figuren.
- Carl Tigerstedt** (Helsingfors): Ein Ventil für direkte Injektion ins arterielle System. Mit 1 Figur.
- Ein Apparat zur Narkose bei künstlicher Atmung. Mit 1 Figur.
- K. Bürker** (Tübingen): Methoden zur Beobachtung und Gewinnung von Blutplättchen. Mit 1 Figur.
- Richard Burlan** (Neapel): Ein Apparat zur Erzeugung von gleichartigen Induktionsströmen (resp. von Kettenstromstößen) alternierender oder gleichbleibender Richtung. Mit 5 Figuren und 9 Kurven.
- A. Lohmann und M. Rinck** (Marburg): Ein Kymographion mit elektrischem Antrieb. Mit 2 Figuren.
- Edgard Zuaz** (Brüssel): Ein etwas verändertes Kroneckersches Herzmanometer. Mit 3 Figuren.
- Dr. W. Fernet und Dr. med. vet. M. Müller** (Straßburg i. E.): Zur Herstellung und Verwendung präzipitirender Sera, insbesondere für den Nachweis von Pferdefleisch. Mit 3 Figuren.
- Dr. K. A. M. Noyons** (Utrecht): Über Modifikationen unpolarisierbarer Elektroden. Mit 2 Figuren.
- Otto Cohnhelm** (Heidelberg): Zur Technik der Duodenalfisteln. Mit 1 Figur.
- Albrecht Bethe** (Straßburg): Präparate von Medusen zu physiologisch-pharmakologischen Versuchen. Mit 5 Figuren.
- T. Graham Brown** (Straßburg): Eine neue Methode, Herzbewegungen bei Tauben zu registrieren. Mit 1 Figur.
- Raymond Pearl Ph. D. und F. M. Surface Ph. D.** (Orono, Maine, U.S.A.): Apparate und Methoden, die bei experimentellen Untersuchungen über Vererbung beim Geflügel gebraucht werden. Mit 11 Figuren, davon 8 auf einer Tafel.
- Gustav Bayer** (Innsbruck): Zur Technik der Produktion von Kreislaufstörungen. Mit 1 Figur.
- Wilhelm Trendelenburg** (Freiburg i. B.): Ein Froschhalter für die Schradersche Labyrinthextirpation. Mit 1 Figur.
- J. K. A. Wertheim-Salomonsen** (Amsterdam): Die Anordnung von Kompensationsvorrichtungen zu physiologischem Gebrauch. Mit 6 Figuren.
- S. Baglioni** (Rom): Ein Nervenmuskelpreparat von Rochen. Mit 1 Figur.
- Dr. med. A. Sulima** (St. Petersburg): Über Narkotisierung von Haifischen. Mit 1 Figur.
- Richard Burlan** (Neapel): Methoden zum Auffangen von Fischharn. Mit 6 Figuren.
- J. P. McGowan. M. A., M. B., B. Sc., &c.** (Edinburgh): Zwei praktische Methoden bei der gerichtlich-medizinischen Anwendung der Präzipitinprobe. Mit 2 Figuren.
- A. Pi Suñer** (Barcelona): Über eine physiologische Lokalisationsmethode in den nervösen Zentren.
- Die Biologische Versuchsanstalt in Wien. Zweck, Einrichtung und Tätigkeit während der ersten fünf Jahre ihres Bestandes (1902—1907), Bericht der zoologischen, botanischen und physikalisch-chemischen Abteilung, zusammengestellt von **Hans Przibram**. Mit 28 Figuren und 1 Plan.

VERLAG VON JOHANN AMBROSIOUS BARTH IN LEIPZIG.

**L**OEB, Prof. Dr. JACQUES, Vorlesungen über die Dynamik der Lebenserscheinungen VI, 324 Seiten mit 61 Abbildungen. 1906. M. 10.—, geb. M. 11.—.

Der berühmte amerikanische Physiologe legt in diesen Vorlesungen seine eigenen Untersuchungen über die Dynamik der Lebenserscheinungen und der Ansichten dar, zu denen sie ihn geführt haben. Eine möglichst vollständige Darstellung des Gebietes der experimentellen Biologie ist erstrebt worden, und die Resultate der neuesten Untersuchungen wurden, soweit es möglich war, eingefügt.

**L**OEB, Prof. Dr. JACQUES, Untersuchungen über künstliche Parthenogenese und das Wesen des Befruchtungsvorganges. Deutsche Ausgabe unter Mitwirkung des Verfassers herausgegeben von Prof. Dr. E. Schwalbe, Heidelberg. VIII, 532 Seiten mit 12 Abbildungen. 1905. M. 7.50, geb. M. 8.50.

Dieser Band enthält die hochinteressanten Versuche über jungfräuliche Zeugung und werden hier vom Verfasser selbst dargestellt. Sie zeigen, daß sicher die Eier der Würmer und Mollusken zur künstlichen Parthenogenese veranlaßt werden, und es scheinen nur noch technische und nicht prinzipielle Schwierigkeiten zu bestehen, wenn irgendeine Grenze für das Gelingen weiterer Versuche besteht.

**L**OEB, Prof. Dr. JACQUES, Die Bedeutung der Tropismen für die Psychologie. Vortrag, gehalten auf dem VI. Internationalen Psychologen-Kongreß zu Genf 1909. 51 Seiten. 1909. Kart. M. 1.—.

**B**RODMANN, Dr. K., Der Zellenbau der Großhirnrinde in der Säugetierreihe. Grundlegung zu einer vergleichenden Lokalisationslehre. X, 324 Seiten mit 150 mikrophotographischen Textabbild. und schematischen Zeichnungen. 1909. M. 12.—.

Münchener medizinische Wochenschrift: Die Ergebnisse einer 8jährigen, ungemein mühevollen und planmäßigen Arbeit hat Brodmann in vorliegendem Buche bekanntgegeben. Das Buch enthält eine Menge von neuen Tatsachen, und es erfüllt das Werk jedenfalls als ein Muster unentwegter wissenschaftlicher Arbeit in heutzutage seltener Weise die alte Forderung des „*nonum prematur in annum*“. Ein dauernder Platz in der medizinischen Wissenschaft ist ihm sicher.

**B**RODMANN, Dr. K., Beiträge zur histologischen Lokalisation der Großhirnrinde. Fünfte Mitteilung: Über den allgemeinen Bauplan des Cortex pallii bei den Mammaliern und Zwei homologe Rindenfehler im besonderen. Lex.-8°. 126 Seiten mit 298 Abbildungen. 1906. M. 9.—

**B**RODMANN, Dr. K., Beiträge zur histologischen Lokalisation der Großhirnrinde. Siebente Mitteilung: Die cytoarchitektonische Cortexgliederung der Halbaffen (Lemuriden). 48 Seiten mit 9 Tafeln. 1908. M. 7.—.

Diese im neurobiologischen Institut zu Berlin gemachten Untersuchungen bilden zugleich Ergänzungshefte zum „Journal für Psychologie und Neurologie“, Band VI bzw. Band X.

**J**ournal für Psychologie und Neurologie. Herausgegeben von August Forel und Oskar Vogt, redigiert von K. Brodmann. In zwanglosen Heften erscheinend. 6 Hefte bilden einen Band, der M. 20.— kostet.

Das Journal will aus dem Gebiet der normalen, pathologischen und vergleichenden Psychologie und Neurobiologie (Anatomie und Physiologie des Nervensystems) solche Arbeiten bringen, die von spezieller Bedeutung für ein anderes der von ihm gepflegten Wissensgebiete oder speziell ärztlich-psychologischer Natur sind, und zwar entweder die psychische Genese, Therapie und Prophylaxe von Krankheitssymptomen oder psychopathologische Probleme berühren.

**F**estschrift zu Forels sechzigstem Geburtstag (Journal für Psychologie und Neurologie. Band XIII). VI, 435 Seiten mit 19 Tafeln und vielen Textillustrationen. 1908. M. 36.—.

Diese, Forel zu seinem 60. Geburtstag von Schülern, Freunden und Verehrern gewidmete Festschrift enthält sehr wertvolle Beiträge zur Neuronenlehre. Mitarbeiter sind: Bernheim, Bugnion, Cajal, Claparède, Domikow, Frank, Juliusburger, Kohnstamm, Moheim, H. W. Maier, Marinesco, Mauss, A. Meyer, F. Mohr, Oppenheim, Peterson, Piltz, Prince, Quensel, Santschi, Semnon, Snessarew, Warnke, Wheeler.

**H**ELD, Prof. Dr. HANS, Die Entwicklung des Nervengewebes bei den Wirbeltieren. IX, 378 Seiten mit 275 Figuren auf 53 Tafeln. 1909. M. 30.—, geb. M. 32.—.

Zentralblatt für normale Anatomie und Mikrotechnik: Über die neurogenetischen Arbeiten von Held ist in diesen Blättern schon des öfteren berichtet. Jetzt hat Held in großzügiger Weise seine Untersuchungen zusammengestellt und baut aus den aus ihnen gewonnenen Beobachtungen seine Lehre von der synzytialen Entstehung der Nervenfasern innerhalb eines Neurenzytiums auf. Es ist damit ein Werk entstanden, das einen Markstein in der Geschichte der Biologie bedeutet, ein Werk, das nicht allein für den Biologen, sondern auch für den Psychiater und Neurologen von fundamentaler Bedeutung ist.

SPLANCHNOPTOSIS, OR CONSTITUTIONAL NEUROCARDIO-  
VASCULAR ASTHENIA WITH OSSEOUS DYSTROPHIES  
AND DISPROPORTIONS.—ENTEROPTOSIS.

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The name of this disease is derived from two Greek words *έντερον*, meaning bowel, and *πτῶσις*, meaning a fall. In its strictest sense, therefore, the term could only be applied to dislocations or prolapsus of the intestine or any part of the bowel. For instance, even prolapsus of the rectum in an otherwise perfectly normal individual could be called enteroptosis, which already indicates the inadequateness of this term. Splanchnoptosis which is derived from the Greek word *σπλάκνα*, meaning viscera, and *πτῶσις*, meaning a fall. Therefore splanchnoptosis would mean the dislocation of any internal organ, but as a fall could only occur downward it would mean only downward dislocations. It is essential to point out these differences of terminology, for there are also upward dislocations of the viscera.

Judged from a more modern and comprehensive view of these conditions, both terms are inadequate and misleading, for the displacement is only a part of the great complex of pathological events that are classed under these terms.

The following are the principle structures that are in an abnormal condition in the state above defined: (1) The osseous structures and joints; (2) the nervous system, especially the autonomic and sympathetic system; (3) the heart and blood-vessels; (4) the organs of digestion and metabolism; and (5) an unknown (cryptogenic) disturbance of internal secretion.

As a result of fundamental changes in these structures we find displacement and prolapsus of the viscera as a necessary consequence. The displacements are not the cause of the manifold symptom-complex, but rather the result of it, if we can speak of a thing being a result that is congenital.

This brings us to another effort at being precise. We really have no right to call a certain position of an organ, when not normal, a ptosis, meaning a falling or prolapsed organ when that organ never has been in normal position. We can only logically speak of a falling or ptosis when an organ descends from a higher to a lower position. This is not the case in genuine enteroptosis, for individuals, who have the evidences of the four deranged states just mentioned—namely, disproportion of the



osseous system, abnormal autonomic nerve function, infirm cardiovascular performance, and displayed viscera, never have been normal and are born with all these infirmities.\* After the original and brilliant clinical studies of Frantz Glénard, the next most important contribution was by Stiller. The broad and fundamental conception of enteroptosis as an inherited constitutional abnormality is one of the great discoveries of the latter.\*\*

According to this clinician, enteroptosis is only a part-phenomenon of a very special form of body constitution, which he designates by the term of *habitus enteroptoticus*. He calls the clinical picture *asthenia universalis congenita*, a very graphic expression, but still not covering all the essential features of the disease. But, as it would be impossible to invent a term which would cover all the manifold morbid entities which are comprised in the complex of symptoms of this disease, the term universal congenital asthenia is recommended as a substitute for the term enteroptosis. Otherwise we should have to designate it as *osseous neurocardiac vascular splanchnic asthenia*.

We now see that enteroptosis is only a restricted and narrow designation. Universal congenital asthenia with splanchnoptosis would represent a more comprehensive term. It is true that the splanchnoptosis is the principle element of the disease when these sufferers present themselves to the clinician, for then they exhibit mainly four abnormal conditions: (1) Lack of tonus in the heart, blood-vessels, and muscles; (2) displacement of one or more of the viscera; (3) neurasthenia; and (4) one or more of the varieties of indigestion, usually the type called nervous dyspepsia.

During childhood the abdominal viscera are not in the same position as they occur in the adult. During puberty the stomach, spleen, pancreas, kidney, and liver rise to the positions which they hold in adult life. In the splanchnoptotic neurasthenic they never rise to their normal position. One of the principle reasons for this failure of the viscera to ascend to the normal position, that is typical in the healthy adult, is a physical impossibility to do so. In the first place, the liver, stomach, and spleen are prevented from occupying as high a position in the splanchnoptotic, because there is no room for them to rise in, owing to the narrowness and elongation of the bony thorax. This the writer has already fully described in his textbook on "Diseases of the Stomach," and furthermore in his work on "Diseases of the Intestines." But for a more recent anthropometric study of the bony structures of the splanchnoptotic, he refers the reader to his investigations published in *Internationale Beiträge z. Pathologie u. Therapie der Ernährungsstörungen*, Vol. 2, No. 3, 1910.

The viscera cannot occupy their normal position, for the simple reason

\*The entire history of the clinical recognition of enteroptosis is given in the writer's work on "Diseases of the Stomach," pp. 693-730.

\*\*Ueber Enteroptose, etc. (*Archiv fuer Verdauungskrank.*, Stuttgart, 1907).

that there is no room for them; and this lack of room is due to disproportion of the osseous structures of the body, this osseous malformation being inherited and handed down from generation to generation. It will be noticed, by this time, that the writer does not distinguish two kinds of splanchnoptosis as other authors do, who recognize an acquired splanchnoptosis and a congenital form. If we understand and appreciate what has been explained in the preceding, genuine asthenic splanchnoptosis cannot be acquired any more than club-foot or harelip. By this he does not mean to assert that persons, who at one time in their lives have their viscera in perfectly normal position, cannot acquire a prolapsus of one or the other of their internal organs; but this should not be then designated as splanchnoptosis, by which is included all the osseous, nervous, and cardiovascular irregularities before mentioned. When a displacement of one particular organ is acquired in an otherwise normal individual, this should be designated by the name of the particular organ that is out of position, and the word dislocation or prolapsus should be used instead of the word ptosis. Thus we might speak of dislocation of the stomach, of the uterus, of the kidney, meaning at the same time that the individual was not born therewith, but developed it in later life, and that the patient is not necessarily afflicted with a simultaneous malformation of the bony framework and infirm circulatory and nervous systems.

*Diagnosis.*—The best means of diagnosing dislocations of abdominal organs are the examiner's fingers, eyes, and ears. No modern technical or laboratory methods have exceeded the practical results gained by the application of the senses of the physician. The eyes to see the abdominal distension, the irregularities of contour, and the location of inflated areas or tumors; the fingers to feel the distension of the hollow organs and dislocation of the solid organs, to palpate their position, to percuss their extent, and to feel the characteristic floating tenth rib of Stiller; the ears to detect the splashing sound after certain manipulations of the colon, stomach, or small intestine. There are other means of aiding diagnosis; for instance, the introduction of instruments into the stomach or colon, which may be recognizable *in situ* either by palpation or the *x*-rays (spiral metallic tube of Turck and Kuhn), or by the electro-diaphane. A means which is very readily at command is the introduction of a long colon tube through the entire colon. Through this the colon can be distended, and by alternately forcing in air and water, the location of the end of the tube can be determined by auscultating on the outside of the abdomen. The writer's experience as a teacher has impressed upon him that there is great danger of young clinicians becoming absorbed in the technical and artificial methods of diagnosing when the natural symptomatology, and the hands, eyes and ears of the examiner often yield better results. They seem to imagine that the results of the examination are not exact unless they are ascertained by some instrumental method. Experienced teachers will bear in mind that 90 per cent. of all the patients who con-

sult the general practitioner object to technical and instrumental methods of diagnosis. The physician himself, as a rule, gratefully accepts any practical means that can reveal the pathological condition of the patient to him; and these are the means which the writer desires to emphasize.

*Changes of Sound in a Stomach Containing Semi-Fluid or Fluid Material, and Produced by Changing the Position of the Patient.*—When a patient, whose stomach contains such material, is placed in the left diagonal lateral position, a dullness is produced on percussion in the left epi-



Funnel thorax with gastropotosis and upward displacement of the heart. The stomach is displaced downward, the heart upward. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

and mesogastric region. This dullness disappears when the patient resumes the recumbent or right lateral position. If the stomach is normal and in correct position, this dullness cannot even be produced immediately after meals. If it can be produced in an abnormally low position, we are confronted with a case of gastropotosis. If it can be produced after the normal digestive period, we are confronted with motor insufficiency. If this sound can be produced five hours after breakfast, or even before breakfast when no food has been taken during the night, we are con-

fronted with a case of dilatation of the stomach with stagnation. When one uses this method of examination frequently, one gradually learns to derive more and more information from it. It is about as valuable as feeling the pulse for the determination of arterial tension and cardiac rhythm. At one time we were in danger of being persuaded that feeling of the pulse with the fingers had no clinical value whatever, and that to find out anything about the heart and circulation everybody must of necessity have a galvanometer of Einthoven or a sphygmograph. We



Funnel thorax (Trichter-Brust) with downward displacement of the stomach but upward displacement of the heart. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

have recovered from this delusion, and so the writer is able to say that the physical signs conveyed to us by our senses are as valuable, if not more so, than the information gained by the technical armamentarium of the laboratory, though he does not mean to be understood as deprecating the latter.

*Splashing Sounds.*—Splashing sounds necessitate the presence in a hollow viscus of liquid and air simultaneously. The stomach when it is dislocated has lost its muscular tonicity, which means that it is in a con-



dition of atony. It cannot contract around the ingesta in the normal manner; on the contrary, it gives way to the pressure and weight of the ingesta, its lower curvature becomes distended and sinks down, its capacity becomes greater, and later on the lesser curvature sinks down also. This is a condition of ptosis developing from simple atony. In simple atony tonic contraction of the stomach is simply weakened, but peristalsis is still effective. A splashing sound does not exactly indicate a gastrop-tosis and enteroptosis in general. Stiller regards the splashing sound as one of the most important signs of this condition. It would lead me too far to differentiate the conditions spoken of as atony, dilatation, and gastrop-tosis. (See Hemmeter's "Diseases of the Stomach.")

*Stiller's Sign: The Floating Tenth Rib.*—Concerning the floating tenth rib, which Stiller proposed as a stigma that, as he claimed, was pathog-nomonic for enteroptosis (*costa decima fluctuans*), much has been written. It occurs in the writer's records in 75 per cent. of the cases of enter-optosis. It is necessary to distinguish between a movable tenth rib and an entirely detached tenth rib. Stiller did not assure himself whether the tenth rib was always normally firmly attached to the costal arch.

Tandler\* and Meinert\*\* state that a loose tenth rib is rather the rule than the exception and that it actually represents the normal condition.

Any persistent narrowing of the lower thorax must eventually force away the tenth rib from its costal attachment. This is the reason why it is so often found detached and widely separated from the ninth rib. It is therefore due to the osseous malformation of the entire thorax with a narrowing of the lower part and the usual emaciation of this class of cases. The demonstration of the floating tenth rib is to Stiller a proof of the existence of asthenic constitutional disease with splanchnoptosis.

Personally the writer regards the floating tenth rib as an unavoidable, concomitant, bony malformation occurring together with an unusually elongated bony thorax. In the article before quoted (*Anthropometric Studies of the Osseous Proportions of the Human Body, with a View to Obtaining a Mathematic Expression for Enteroptosis*) he has proposed the infraxyphoid angle as a diagnostic criterion for splanchnoptosis. The reason for that must be apparent on reading that article, for it is there shown that this angle is the index of the diameter of the thorax. When that article was published the writer had made measurements of the bony frame of 1,125 splanchnoptotic patients. The measurements which he recommends are the following. He repeats also a table giving the dimensions of these measurements in 810 cases of females and 315 cases of males in order that some idea of the figures to be expected might be obtained.

Hitherto there has been only one mathematic index proposed for en-

\**Wien. klin. Wochenschr.*, No. 8, p. 200, 1900.

\*\**Wien. klin. Wochenschr.*, No. 2, 1900.

COMPILATION OF 810 CASES FEMALES.

Anthropometric proportions in relation to enteroptosis. (Female.)	HEIGHT IN FEET.										
	5'	5' 3"	5' 4"	5' 5"	5' 6"	5' 7"	5' 8"	5' 9"	5' 10"	5' 11"	5' 11½"
M to X (Means distance from the manubrium to the xyphoid cartilage) .....	16 <sup>2</sup> / <sub>3</sub>	17 <sup>11</sup> / <sub>18</sub>	19	18	18	19	19	20	21	21	22
M to U (Means the distance from the manubrium to the umbilicus) .....	31 <sup>4</sup> / <sub>9</sub>	32 <sup>1</sup> / <sub>9</sub>	32 <sup>4</sup> / <sub>11</sub>	33	33	34	34	35	36	38	40
M to S (Means the distance from the manubrium to the symphysis) .....	48	49 <sup>7</sup> / <sub>9</sub>	50 <sup>8</sup> / <sub>11</sub>	54	53	52	53	53	54	56	57
X to RAS (Means the distance from the xyphoid to right superspine ileum) .....	26 <sup>5</sup> / <sub>9</sub>	27	25	28	28	27	29	30	30	30	31
X to LAS (Means the distance from the xyphoid to left superspine ileum) .....	27 <sup>2</sup> / <sub>9</sub>	26 <sup>13</sup> / <sub>18</sub>	27	27	28	27	28	31	30	29	30
R to LAS (Means the distance from right to left anterior and superior spine ileum) .....	24 <sup>5</sup> / <sub>9</sub>	25 <sup>5</sup> / <sub>9</sub>	25	28	27	27	28	30	30	30	31
Circum. at X (Means circumference at xyphoid) .	65 <sup>8</sup> / <sub>9</sub>	68 <sup>7</sup> / <sub>9</sub>	68	67	66	67	70	71	73	74	76
Atlas to 5 Lumbar .....	58 <sup>1</sup> / <sub>9</sub>	58 <sup>2</sup> / <sub>9</sub>	56	66	65	66	69	70	71	72	75
Height (in centimetres) .....	152,4	160,0	162,5	165,0	167,6	170,1	172,7	175,2	177,7	180,3	182,8
Weight (pounds) .....	110 <sup>2</sup> / <sub>9</sub>	125 <sup>1</sup> / <sub>2</sub>	121	119	125	125	135	144	150	150	160
X-Angle (Means the angle below the xyphoid, Infrasternal) .....	66	68	68	69	69	70	70	72	73	73	75

The average (plurimum) dimension of the infraxypoid angle in normal females varies with the height (stature) and age.  
The average normal female xypoid angle at an age of 30 and stature of 5 ft. or 152,4 cm. is 80,2 degrees (318 measurements).

COMPILATION OF 315 CASES OF MALES.

Anthropometric proportions in relation to enteroptosis. (Male.)	HEIGHT IN FEET.													
	5'	5' 1"	5' 2"	5' 3"	5' 4"	5' 5"	5' 6"	5' 7"	5' 8"	5' 9"	5' 10"	5' 11"	5' 11½"	
M to X (Means distance from the manubrium to the xyphoid cartilage).....	18	19	19	19	20	20	20	21	22	23	23	24	24	
M to U (Means the distance from the manubrium to the umbilicus).....	32	32	34	34	34	34	35	36	36	38	38	39	40	
M to S (Means the distance from the manubrium <sup>1</sup> to the symphysis).....	50	51	51	50	52	53	53	54	54	56	57	59	60	
X to RAS (Means the distance from the xyphoid to right superspine ileum).....	27	27	28	28	28	28	29	29	30	31	32	32	32	
X to LAS (Means the distance from the xyphoid to left superspine ileum).....	26	27	28	27	28	27	29	30	30	30	31	32	33	
R to LAS (Means the distance from right to left anterior and superior spine ileum).....	27	27	27	28	27	28	28	30	30	30	31	32	33	
Circum. at X (Means circumference at xyphoid)...	69	70	73	72	74	76	76	77	78	80	79	80	80	
Atlas to 5 Lumbar.....	66	68	69	69	70	70	71	73	73	75	75	76	78	
Weight .....	130	136	155	131	133	153	140	146	150	150	170	170	180	
X-Angle (Means the angle below the xyphoid. Infrasternal) .....	68	69	69	69	70	71	72	73	73	74	75	75	76	
Height in centimetres .....	152.4	154.9	157.4	160.0	162.5	165.0	167.6	170.1	172.7	175.2	177.7	180.3	182.8	

The measurements are in the metric system (metres and centimetres). The angle is expressed in degrees of a right angle. The weight in pounds.

The average (plurimum) of the infraxyphoid angle in males varies with the stature and age. At age of 30 years and at a stature of 5 ft. or 152.4 cm. the average male infraxyphoid angle is normally 84 degrees (320 measurements).

teroptosis, the Becher-Lennhof index for *asthenia universalis congenita*. This is obtained by dividing the distance of the jugulum from the upper edge of the symphyses by the number expressing the smallest circumference of the abdomen and multiplying the quotient by 100. It is a purely empirical procedure and has given no results that could be called even approximately reliable. The unreliability of the average of this index, which for the normal female body in dorsal position is 75, is that one of the factors is extremely variable—namely, the abdominal circumference. This may vary 4 to 5 cm. in the same individual on the same day, according to the distension of the stomach and intestines by food, gas, feces, etc.

For males, the average of this Becher-Lennhof index is less than 75. A high index, over 80, is found in persons with palpable kidneys and the asthenic enteroptotic constitution. Before we knew that Becher and Lennhof had proposed it, we had already tried it and discarded it because of its extreme variations in normal persons.

*Displacement of the Thoracic Viscera in Splachnoptosis.*—In the article quoted (*Anthropometric Studies*, etc.) there is a chapter entitled, "The Position and Dimensions of the Organs of the Thorax in Enteroptosis," and it is accompanied by three *x*-ray illustrations showing the low position of the heart in these cases as compared with the normal position. These positions can without difficulty be demonstrated by the othodiagraph of Franz M. Groedel. Since the publication of this article, further cases of splachnoptosis with displaced hearts have been published by the writer's associate, Dr. Albert H. Carroll. As far as the diaphragm and the osseous limitations of the thorax will permit it, the heart is as a rule dislocated downward in all cases of splachnoptosis, and the arch of the aorta is elongated producing what is called pendulous heart. The technical difficulties of *x*-ray photography of the thorax have all been taken into consideration in determining these positions.

*The Esophagus* is always unusually elongated, which should not surprise us when we reflect upon the elongation of the entire thorax. External measurements of the thorax, by means of Prof. W. Scott Hall's chest pantograph, always show an abnormally narrow thoracic contour; the thorax being compressed, as it were, both in an anteroposterior as well as in a lateral direction. The writer has seen one man in whom the distance between the xyphoid cartilage and the spinous process of the dorsal vertebra was only 3 in. These measurements usually do not meet with the appreciation they deserve by the general practitioner. The Hall chest pantograph is an instrument which can be very easily manipulated, and its application to splachnoptosis cases gives an idea of the depth and width of the thorax, which can be acquired in no other way. The outlines obtained are very objective, graphic, and convincing. The diagnosis could be made from them alone, together with the measurements of the infraxyphoid angle which the writer regrets to state is already



being designated by his name. It is far preferable that this angle should be named by its correct anatomical designation.

*Use of X-Ray for the Diagnosis of Splanchnoptosis.*—Over fifteen years ago, the writer published the first method\* by which the  $x$ -rays were used to photograph the human stomach in totality. The article is entitled "Photography of the Human Stomach by the Roentgen Ray." It is true that Wegele had in the same year suggested the introduction of a metallic spiral electrode into the stomach in such a manner that it should come to lie along the greater curvature, and that the  $x$ -ray method would show this spiral electrode in the photograph. Of course, this shows only the greater curvature and not the entire stomach. But the method above suggested by the writer (l. c.) is the first one to make it possible to photograph the stomach in its entirety. Such  $x$ -ray photography may be undertaken for the amusement of the investigator or for the sake of experimentation, but for arriving at a definite diagnosis the method is not necessary. It may even lead to serious error which is evident from the work of Rosenfeld,\*\* and Grædel.† These men believed to have proved that in genuine gastropotosis it is not the entire organ that is sunken, but only the pylorus, and even Elsner†† claims every gastropotosis to be nothing but a pyloroptosis, and that the displacement of this section of the stomach must necessarily be accompanied by a dilatation. Elsner is very emphatic in siding with Rosenfeld that there is no such thing as gastropotosis without dilatation of the stomach. Anatomically, therefore, these authors consider gastropotosis nothing but a sinking of the pylorus with a dilatation of the stomach between the cardia and the pylorus.

As it is well known that dilatation of the stomach cannot exist without giving rise to symptoms, this statement of Elsner's is in striking contradiction with another statement by him on p. 450 of the same book, where he quotes Stiller as emphasizing that persons with splanchnoptosis may enjoy perfect health for years; and Elsner adds that this statement is made *mit Recht*. The writer considers the results of Rosenfeld and Grædel as one of the serious errors that has resulted from the idolatry of  $x$ -ray diagnosis in abdominal diseases. Neither of these men could have studied the place in Riegel's "Diseases of the Stomach," where splendid illustrations are given of prolapsed stomachs located at or below the navel, not only without any dilatation whatever, but actually very small in size. The writer has included one of the illustrations in his own textbook on "Diseases of the Stomach" demonstrating this point.

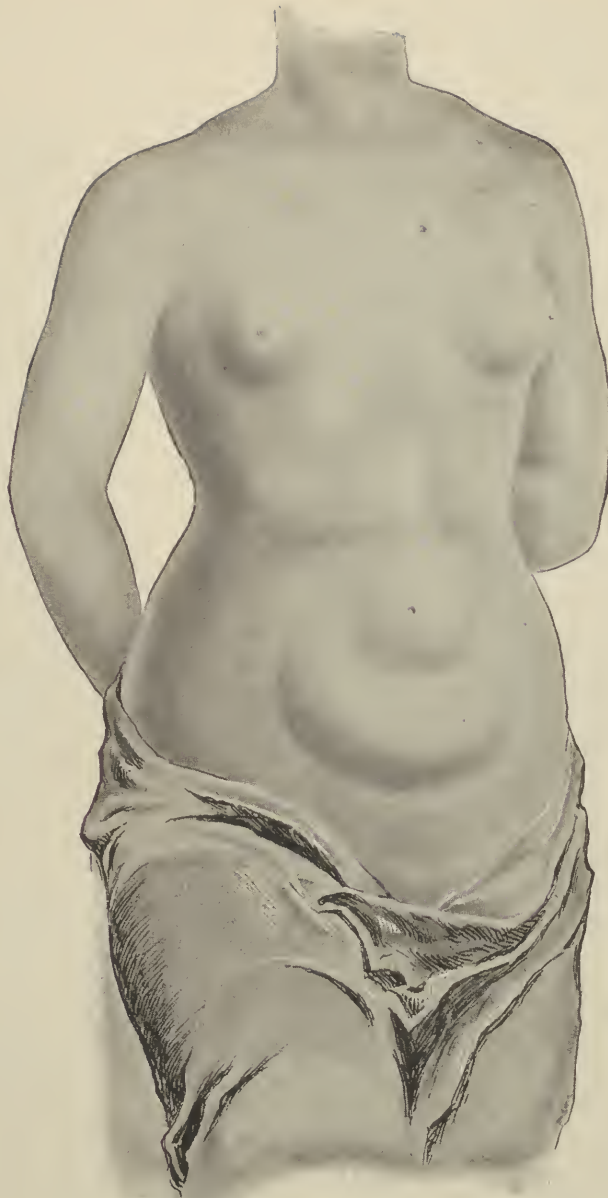
It becomes the writer's duty to emphasize here that Frantz Glénard already knew that in gastropotosis the stomach can be simply displaced and not necessarily dilated. The works of this keen diagnostician should be read with greater frequency, for although the German clinicians have

\**Boston Medical and Surgical Journal*, June 18th, 1896.

\*\**Zentralbl. fuer inn. Med.*, No. 1, 1899.

†*Med. Klin.*, 9, 1908.

††*Lehrbuch der Magenkrankheiten*, p. 436.



Gastropotosis with right nephrotosis. Bony thoracic measurements normal. Subxyphoid angle normal, hence not a typical case of the congenital type of splanchnoptosis but acquired and caused by tight lacing. (From Hemmeter's Diseases of the Stomach, by permission of Messrs. P. Blakiston's Son and Co.) From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

expanded the clinical conception of splanchnoptosis and perhaps disproved some of Glénard's minor contentions, it is due to him that modern medicine was enriched by accurate scientific description of one of the broadest symptom-complexes that occurs in clinical pathology.

*Effect of Splanchnoptosis in Producing Compression of the Blood-Vessels, Especially the Veins of Displaced Organs.*—Bearing in mind that the veins have more compressible walls than the arteries, it is intelligible how they are more obliterated than the former when an organ becomes dislocated. The very dislocation produces a forced position of the blood-vessels contained in the organ. This is especially true in the stomach and colon. The arteries are capable of conducting as much blood into the displaced organs as occurs when the organ is in normal position, but the veins cannot carry away as much blood as is conducted into the organ. The consequence of this is that, in organs that are decidedly misplaced, there is a continual passive congestion due to the incapacity of the veins to lead off the blood that enters in a given time through the arteries. This chronic hyperemia is in my opinion the principle cause of the frequent catarrhs of the stomach, the intestine, and colon. Even the well-known membranous colitis, which is met with frequently in splanchnoptosis, particularly coloptosis, is in its incipency, at least, produced by this altered circulation.

*Nephroptosis.*—The most exaggerated circulatory disturbances that are met with in this condition are found in extreme cases of dislocation of the kidney—nephroptosis—where the vessels may actually be twisted off, so that we can find cases of floating kidneys recorded where the ureter was completely obliterated by a kink or twist, and where even at the operation the renal vein appeared to be almost obliterated. Where such conditions as these exist, the only hope of relief comes from replacing the organ to its normal position, and in such cases a surgical procedure to fix the loosened kidney in its normal position may be a life-saving measure. Fortunately, the necessity for surgical treatment is rare even in kidney dislocations of which various degrees must be differentiated—namely, (1) the palpable, (2) the movable, (3) the floating kidney. For dislocation of the stomach and colon, surgical operation is exceedingly rarely called for; and, in those cases in which operation was undertaken, in the writer's experience the symptoms did not disappear, and an alarmingly large proportion of the operated cases gave later evidence that the organs had again detached themselves from the location in which they had been artificially fixed. A treatment which aims at fattening of the patient has given more satisfaction to the patient and more permanent relief than any of those which he had operated.

*Pathology and Causation.*—When the writer states that in his opinion the genuine splanchnoptosis is always congenital, he is aware that this explains very little; and yet it is about all that can be definitely said of the etiology of splanchnoptosis, for all the rest that has been advanced

in explanation of this peculiar condition is nothing but speculation and hypothesis. Rosengart's theory\* explains splanchnoptosis as a pathological reversion of the location of the abdominal organs to an embryonic state. There is nothing new in this, nor does his statement differ essentially from the expression that the condition is congenital; for congenital means that the condition exists before birth and therefore is an embryonic state. Outside of this theory there are mainly two others that could interest us. First, that of Weisker,\*\* according to whom the abdominal organs are carried by ligaments and mesenteries, and the firmness and rigidity of these determines and maintains the equilibrium of things within the abdomen. We could understand this if there were ligaments strong enough to support such an organ as the liver. All the ligaments in the abdomen put together could not hold such a heavy organ as the liver in position if the only support were by ligaments. But the manner in which the liver is maintained in position can be ascertained by the following experiment. Open an abdomen at autopsy, and through a small hole insert the hand and forearm, and grasping the vessels on the under surface of the liver attempt to pull it down. All the strength of an average man will not suffice to do it, that is provided the subject did not have enteroptosis and was otherwise normal. The liver is held up against the diaphragm by a negative pressure similar to the negative pressure that holds the head of the femur in the socket of the acetabulum. Dissect all the ligaments away from this articulation on a dead subject, and the spherical head of the femur will still be retained in its socket. It is not the ligaments alone that keep the head in its socket, but the negative pressure. The same is true of the liver, and this being the largest and heaviest organ in the abdomen it is plausible that it should be capable of supporting whatever other organs are anatomically attached to it. The second theory, besides Rosengart's, is advocated mainly by Schatz and Leshafft† who hold that the abdominal organs are kept in place exclusively by intra-abdominal pressure, and that the ligaments do not play a very essential part in their support. A third group of authors, Schwerdt,†† Quincke‡ and Meltzing‡‡ occupy an intermediate position between those that hold that the abdominal organs are supported by ligaments and those that hold that they are supported by negative atmospheric pressure. It is not clear how the abdominal muscles could support all the abdominal organs in position, for the main force of the contraction of these muscles is, according to the writer's experiments, exerted at a point about midway between the xyphoid cartilage and the umbilicus. Accordingly, the contrac-

\**Zeitschr. fuer diät. und physic. Therap.*, Vol. I, p. 220.

\*\**Schmidt's Jahrb.*, Vol. 219, 1888.

†Quoted from Mathes, *Archiv fuer Gynækol.*, Vol. 77.

††*Deutsch. med. Wochenschr.*, 1896.

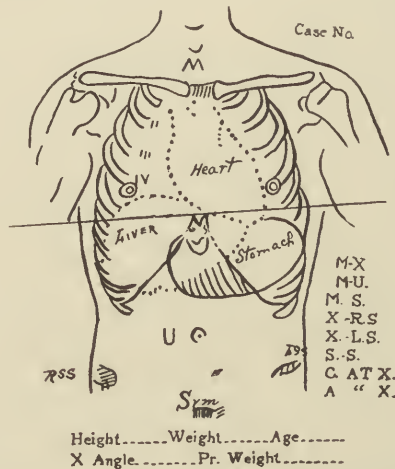
‡*Therapeut. d. Gegenw.*, 1905.

‡‡*Archiv fuer Verdauungskr.*, Vol. IV, p. 181.



tion of these muscles and their normal tonus could keep in position the organs that are above this point,—for instance, the liver, stomach, and spleen; but one could not understand how the abdominal recti muscles could keep the colon in its proper position.

*The Rôle of the Thoracic Respiratory Muscles and the Diaphragm as Supporters of the Abdominal Organs.*—It will at first sight seem paradoxical, to one who has not thought deeply over the problem of splanchnoptosis, how the normal functioning of muscles of the chest should be capable of keeping, in proper position, heavy organs of the abdomen, which are below the chest, and yet this is exactly what is true. Physiologists recognize and have calculated the force of the negative aspiration of the thorax; but this is only spoken of in so far as it favors the reflux of venous blood to the right auricle. But it is not yet recognized to be



Stamp for recording osseous anthropometric proportions in splanchnoptosis cases. Below M, the infraxiphoid angle. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

a physiological fact that the tonicity of the respiratory muscles and of the diaphragm is the principal factor in maintaining the negative pressure that keeps the abdominal organs in position. The writer cannot go into the experiments which prove this point physiologically, but must limit himself to the statement that a strong muscular development of the thorax causes a high position of the arch of the vaulted dome of the diaphragm, and accordingly a larger part of the abdominal viscera will be contained within the bony part of the thorax. It is for this reason that he has selected thoracic measurements as indications for splanchnoptosis, and that he has chosen the infraxiphoid angle as the clinical index for this condition.

If there is such a malformation of the thorax that the diameters become narrower and narrower towards the lower part of the chest, less

and less of the abdominal contents can find room within the bony walls of the thorax. The diaphragm does not represent a vaulted arch, but its curve becomes flatter and flatter, indicating that the thorax is elongated and narrow, and the thoracic organs too low. A deeper understanding of the physiology of the aspiration of the thorax will give an insight into the method of operation by which a strong chest development becomes a factor in supporting the abdominal organs and an infirm bony thoracic development is one of the causes of splanchnoptosis.

*The Factor of Physiological Tonus or Tonicity as a Cause of Maintaining the Viscera in Normal Position.*—Brondgeest showed that if a frog is suspended after removing his brain, both hind legs will assume the same position; but if, in such a decapitated frog, the sciatic plexus in the left leg is cut, the leg on the left side will hang down almost straight whilst the leg on the uninjured side takes a more flexed position. The explanation offered is that the muscles on the sound side are continually receiving impulses from the motor neurons in the cord. Inasmuch as this experimental result cannot be obtained in a frog in which the posterior nerve-roots have been destroyed, it appears evident that this tonic discharge from the motor neurons is due to a constant inflow of impulses from the sensory paths. Muscle tonus, in other words, is in reality a reflex tonus which differs from the ordinary reflex movements only in the absence of a sudden visible contraction and in the more or less continuous character of the enervation. All the voluntary or striped muscles, the heart and the blood-vessels, are in this state of permanent tonus. But the unstriped or plain muscles all over the body also have the power to remain in tone; that is, they are in a continuous state of more or less contraction which is due to stimulations received from the nervous system; and, if thus conceived, this is spoken of as neurogenic tonus. But unstriped or plain muscles such as surround the stomach and intestines will exhibit of tonus to a very marked degree when removed completely from the body. In another work, the writer has given the experimental method by which this intestinal muscle tonus can be tested in the laboratory, based upon the researches of Cannon, who first called attention to the fact that the tonicity of intestinal muscle could be influenced by the amount of suprarenalin in the circulating blood; and, furthermore, that this suprarenalin was under the control of the autonomic system (Dreyer, Meltzer, Langley). For Cannon gave the evidence that emotional excitement caused the secretion, into the blood of the vena cava near the liver, of adrenalin, so that blood drawn from this neighborhood in a cat, after the animal had been excited or frightened, would arrest the rhythmic contractions of intestinal muscle that had been recorded during suspension in blood from a normal cat. When we reflect that splanchnoptosis is invariably associated with irregularities of the autonomic nervous system, we will begin to appreciate the far-reaching value of these observations of Cannon, which would lead us to wish for a biological method of testing

the blood of splanchnoptosis cases for the amount of adrenalin contained in it; for few things are more certain about splanchnoptosis than that the tonus of all the organs provided with involuntary or plain muscle is very much lowered. This accounts for the low arterial pressure that is regularly found in this class of sufferers after they have once begun to be sufferers, also for the flabby state of their muscular apparatus, the inertia of the muscular coat of the stomach and intestines, the loss of tonicity of the respiratory and abdominal muscles.

*Relation of Splanchnoptosis and Vagus Tonicity. Theory that*



Coloptosis. The displacement of the transverse colon is shown by the irregular dark and wavy outline above the black square marking the umbilicus, ten hours after ingestion of Hemmeter calcium carbonate test-diet for *x*-ray photographing. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

*Splanchnoptosis is Due to Hypertonicity of the Vagus Nerve.*—In the eager search for some rational explanation of the pathogenesis of splanchnoptosis, a number of very curious hypotheses have been evolved. The most recent of these is that which would explain this morbid entity by assuming that it is due to a hypertonicity of the vagus. The writers on this subject who convey this idea do not use the word "hypertonicity," but simply call it *vagotonie*, which means vagus tonus. As every physiologist and clinician knows, the vagus is normally and always in a tonic state. We can judge this particularly well by the effect of section of the vagus on

the rate and force of the heart, but it can also be studied by the effect of the same exclusion of vagus function on the peristalsis of the stomach and intestines in some animals, and by its effect on gastric secretion. So with regard to secretion and peristalsis, as well as heart-action, the vagus is normally in a state of continual tonus. What Eppinger and Hess\* mean is an excessive state of vagus excitability; and, as they expressly state that their so-called *vagotonie* patients frequently



Displacement of heart in splanchnoptosis. The stomach is filled with a deposit of calcium carbonate and calcium phosphate in oatmeal. These calcium salts are, in our opinion, as serviceable in roentgenograms of the stomach as is bismuth; are non-poisonous, and are seldom followed by obstipation. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

have the signs of enteroptosis, it will interest us to discuss this hypothesis briefly. The so-called vagotonic constitution is also the expression of an inherited abnormality found in males as well as females who give the external indications of nervous patients. The color of the face alternates rapidly. Sudden blushes alternate with striking paleness. The

\*Die Vagotonie, Berlin, 1910.



hands are bluish red, moist, cool; the individuals frequently enter upon curious sweats. Generally they are under-nourished patients with pale conjunctivæ.

The patients describe much saliva to be gathering in their mouth continually, so that they are often compelled to make swallowing efforts. The tonsils and follicles of the tongue are enlarged. If these symptoms thus far mentioned are correct, they are mainly interesting because not one of them could be referred to hypertonicity of the vagus. But a more striking discrepancy is found in the following statements—namely, that the pharyngeal reflex is absent in most cases, and that the action of the heart is excited (*die Aktion des Herzens ist meist aufgeregt*). How these two signs could be attributed to hypertonicity of the vagus is a physiological conundrum which we must leave to the authors of this hypothesis for an explanation. The afferent nerve-fibres concerned in the pharyngeal reflex are the sensory fibres from the mucous membrane of the pharynx and esophagus contained in three nerves—namely, the glosso-pharyngeal, the trigeminal, and the superior laryngeal from the vagus. But if the vagus is in a state of hypertonicity the reflex should not be “mostly absent,” but should be much more easily obtained than normally.

Still more puzzling is the statement that the heart-action is excited, for if the vagus is in a hypertonic state the heart-action should be slow. The disturbances in the gastro-intestinal canal are described as follows: esophagospasm, which is supposedly due to a hypertonicity of the vagus, but as the esophagus receives motor fibres from the hypoglossal to its upper segment and from the vagus and spinal accessory to the lower segment, it is not clear why esophagospasm should be attributed to the vagus alone, and why it should be coupled in the same individual with marked atony of the stomach and bowels, for the stomach and intestines also receive their motor fibres from the vagus. The inhibitory fibres are received from the splanchnic.

In a recent article, Zweig\* asserts that the above symptoms bear an extraordinary similarity to those of enteroptosis, and that we must attribute all these conditions to an abnormally heightened irritation of the vagus. Inasmuch as hyperacidity and pyrosis are frequent symptoms of enteroptosis, according to this author, he is satisfied that his conclusion is correct, because the administration of atropine relieves both the supposed spasm of the esophagus as well as the hypersecretion.

Whilst pharmacological interpretations of pathological processes are sometimes successful, it is not always logical to depend upon them exclusively. As the writer has already pointed out, splanchnoptosis cases frequently have loss of gastric secretion, even absolute achylia gastrica, and instead of spastic obstipation we frequently have atonic obstipation. Much more puzzling is the generalization of Zweig (l. c. p. 43) in which

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\*Die Pathologie und Therapie der Enteroptose und ihre Beziehungen zu Allgemeinerkrankungen. Albu's Sammlungen, etc., Halle, 1911.

he brings the glands with internal secretion in a causative connection with a permanent hypertonicity of the vagus. This would not mean that the glands with internal secretion are supplied by vagus fibres, but reversely, that they secrete something which maintains the lasting hyperirritability of the vagus. The first assumption, if Zweig be quoted correctly, is manifestly erroneous. He does not state in so many words that the glands with internal secretion are supplied by the vagus, but rather that they produce something which keeps the vagus permanently in a state of hypertonicity; and he compares this hypothetic substance with the adrenalin which is the normal chemical stimulator of the sympathetic system, and he theorizes on the possibility of a hormone occurring in the body which is an antagonist to adrenalin, and which is a normal stimulus to the vagus action. He presumes that this chemical substance, the antagonist to adrenalin, is the substance which keeps the entire autonomous nervous system, including the vagus, stimulated.

This hypothesis has much about it which is fascinating, but it lacks sufficient chemical basis. We are even as yet in the dark as to the manner in which the chemical hormone, adrenalin, and the terminal synapses of the sympathetic fibres co-operate. All that we know is that they do co-operate, but not always how.\*

Opposed to vagus hypertonicity he conceives of a hypertonicity of the sympathetic system, and calls it *sympathicotonie*, which he conceives to be associated with symptoms opposed to *vagotonie*—namely, atony of the esophagus, which assumes that the sympathetic is the inhibitory nerve of the esophagus. No such anatomical distribution of the sympathetics has been as yet described. Secondly, he classes under *sympathicotonie* hypermotility of the stomach, which erroneously assumes that the sympathetic is the motor nerve of the stomach; and, thirdly, he classes under this excessively irritable state of the sympathetic nervous system, *achylia gastrica*, which again assumes that the sympathetic is the inhibitory nerve to the secretion of the stomach.

There is a chemical substance of very simple structure, which does play an important rôle in co-operating with the terminal synapses of the vagus in the heart-muscle. This is potassium chloride. Not only is inhibition of the heart produced more readily when the amount of potassium is increased in the blood circulating through the coronary arteries, but it is assumed that stimulation of the vagus causes a setting free of potassium from the heart-muscle during inhibition. The difference between the manner of action of adrenalin and that of potassium chloride is this,—that adrenalin imitates the action of the sympathetic nerves on any tissue supplied with these nerves (Langley), no matter where in the body these nerves occur. The tissues themselves do not produce adrenalin. It is only produced in the adrenal glands. But with regard to vagus inhibi-

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\*See Hemmeter's Manual of Practical Physiology: Chapter on Internal Secretion.

tion, the potassium chloride is supposed to be set free from the heart-muscle itself. It is not always liberated from the myocardium but only during inhibition.

It is obvious that hypotheses, attempting to explain splanchnoptosis on a purely chemical theory, must be based upon chemical facts, which



Displacement of the heart in splanchnoptosis. The right kidney in the colon transversus was also displaced in this case. (On account of reducing the picture, a photographic "situs inversus" has taken place.) From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

means that we must obtain our chemical substance first, demonstrate its effect on the viscera, nerves, blood-vessels, etc., and construct the hypothesis afterwards. All hypotheses that are not founded on chemical facts simply complicate matters. The surest path to a chemical theory explain-

ing the pathogenesis of splanchnoptosis has been outlined in what the writer had to say concerning the relation of tonicity of the gastro-intestinal tract and blood-vessels to the secretion of the adrenal glands and the stimulation of the peripheral ends of the splanchnic nerves, pp. 262-263 of this article.

*Reflex Time in Splanchnoptotics.*—The nerve centres in the spinal cord co-operate in reflex movements; and a determination of the total time between the application of a stimulus and the beginning of the response gives a means of ascertaining the time needed for the processes within the nerve-cells. In 1898, the writer began a series of experiments on the reflex time of splanchnoptosis cases, which he neglected to continue until in moving to a new location his old notes were rediscovered. They aimed at a comparison between the reflex time of normal individuals and those of splanchnoptosis cases. The method was that usually followed by physiologists—namely, measuring the time elapsing between the beginning of a stimulation and the beginning of contraction, and subtracting from it the latent period of the muscle and the time taken by the stimulation to travel centripetally through the sensory and centrifugally through the motor nerves. Exner had obtained the figure 0.031 seconds as the true reflex time for man and Mayhew\* the figure 0.042 seconds. The writer's own experimental observations, conducted according to the regular methods used in the physiological laboratory,\*\* gave him for splanchnoptosis cases the average figure of 0.0582. This is a sufficient prolongation of the ordinary reflex to suspect an abnormal slow neurogenic process in the neurons of the cord.

*Inhibition and Augmentation, or Reinforcement of Reflexes in Splanchnoptosis.*—It is a well-known physiological fact that normally spinal reflexes can be suppressed entirely by other nerve impulses reaching the same part of the spinal cord. As long ago as 1863, Setschenow (Berlin, 1863) demonstrated this inhibition of reflexes in a frog from whom the cerebral hemispheres had been removed. When he stimulated the cut surfaces of the exposed hind brain by crystals of sodium chloride, the usual spinal reflexes that could be obtained by cutaneous stimulation in a normal frog were, in this brainless frog, greatly depressed. On removing the stimulating substance from the cut surface by washing with a current of normal salt solution, the reflex activities of the cord were again exhibited in the normal way. Many other facts could be cited which indicate that the brain may inhibit the activities of the spinal centres and make it probable, that a definite set of inhibitory fibres exists, arising in parts of the brain and which are distributed to the spinal cord, and that the function of these fibres is to control the activities of the spinal centres. It is conceivable, however, that this brain influence of in-

\**Journ. of Experimental Medicine*, pp. 2-35, 1897.

\*\*See Hemmeter's *Manual of Practical Physiology*, 1912.



hibition may be exerted by some variation in the time relations, quality, and intensity of the nerve impulses, which are of a chemical nature, though neither the separate existence of inhibitory cerebral fibres to the cord nor of a chemical co-ordination has been as yet demonstrated; but the physiological fact of the inhibition of reflexes by the brain has been well established.



Displacement of the heart in splanchnoptosis. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

In the phenomena which the writer has already described as a de-layer reflex in splanchnoptosis, this effect may be due to a primary impediment in the spinal neurons themselves as well as to one of the forms of inhibition just referred to. It is very difficult to decide this point in human beings—namely, whether we are dealing with delayed neurogenic

process in the spinal neurons or an exaggerated inhibition exerted by the brain.

*Augmentation of the Reinforcement of the Reflex in Splanchnoptosis.*—If in a splanchnoptosis case the exact intensity of a single induction shock is determined, which is just sufficient to bring about the patellar reflex, it will be found that the reflex time varies greatly according to the varying conditions of the patient, especially the varying conditions of the spinal cord. There are periods in which the reflex time is shortened and periods in which the reflex time is delayed, though the delay is in more than two-thirds of all cases found to be the rule. The entire phenomena of all reflexes in splanchnoptosis cases give the impression as if the patient were at times under the antagonistic influences of two opposing toxins. One, for example, simulating strychnine and the other opium. The whole matter of the condition of the neurons in the cord of splanchnoptosis cases urgently calls for investigation from the standpoint of the physiologist.

*Diagnosis.*—After what has already been said concerning the diagnosis, the writer may be permitted to be brief concerning this point. As a matter of fact, diagnosis of enteroptosis is rarely difficult. This is particularly true of those dislocations that affect the stomach. Here the simple distension of the stomach by air through a stomach-tube, or by CO<sub>2</sub> gas generated by making the patient drink two solutions, first, one of tartaric acid in water (an even teaspoonful) and after this a solution of bicarbonate of soda (an even teaspoonful), will be sufficient to demonstrate the position. X-ray photography, which the writer practices frequently through his assistants and the electric transillumination of the stomach, is interesting when scientific studies have to be made for the purpose of publication; but the general practitioner and even the specialist can usually dispense with these methods. But in all cases, he would recommend taking the bony measurements which have been heretofore mentioned, and particularly making a record of the angle below the xyphoid cartilage. The chemistry of the stomach should be studied because it calls for varied methods of treatment. Some gastropoptosis cases have no secretion of gastric juice whatever. Some have a hypersecretion, and much comfort can be given by proper attention to the chemistry of the stomach, which in one case may be accomplished by giving dilute hydrochloric acid and in another case may be accomplished by giving alkalies. It depends upon what the chemical analysis reveals.

For the colon the distension with air or CO<sub>2</sub> gas is also a valuable diagnostic method.

For the determination of displacement of other abdominal organs, palpation and percussion yield the best diagnostic results. Next to the stomach and colon we are most frequently confronted with dislocations of the kidney. Here we must distinguish four degrees of dislocation:\*

\*Israel (*Berl. klin. Wochenschr.*, 9, 1899).

*Nephroptosis*.—First degree: The kidney is palpable at the height of inspiration, but disappears after expiration. This degree of renal movability is normal; second degree: The entire kidney can be palpated at the height of inspiration, but it rises again during expiration. In this stage the kidney still exhibits respiratory excursions; third degree: The kidney is found as a palpable tumor below the edge of the ribs but does



Coloptosis and compression of the sigmoid flexure. The left side of the patient is on the right side of this x-ray photograph. From Prof. Hemmeter's Clinic, University of Maryland, Baltimore.

not show any respiratory excursion whatever, nevertheless it can still be passively pushed back under the arch of the ribs; fourth degree: The kidney is fixed below the arch of the ribs and can no longer be pushed back into normal position. To this the writer might add a fifth degree in which the kidney is similar to the degrees three and four, just de-

scribed, but can be moved about almost anywhere in the abdomen and eventually give rise to kinking off of the ureter.

*Dislocations of the Liver, Hepatoptosis.*—There are various degrees of this condition, and one could almost classify them similarly to the classification just given for the kidney dislocations. They can be diagnosed by the methods of palpation and percussion.

*Spleno-ptosis.*—Uncomplicated dislocations of the spleen are very rare. The spleen is normally not a heavy organ, and the pressure of the liver is not exerted upon it; therefore, it is not so frequently dislocated as the kidney. When the spleen is found dislocated and enlarged, it is more often due to organic disease like malaria, syphilis, tuberculosis, cancer, and Banti's disease.

*Symptomatology.*—(a) Subjective Symptoms. Though admirable advances have been made in our methods of comprehending this singular and striking condition since the time of Virchow, Glénard, Ewald, and especially by the recent beautiful clinical investigations of Stiller, we are yet far from fully understanding it. In fact, we are just beginning to have an insight into the profound nervous, organic, vascular, visceral, osseous irregularities which characterize the fully developed type of splanchnoptosis. A human pathological entity like this begins in the fundamental disposition of the germ-layers of the embryo—in fact, one could say without exaggeration that it begins in the embryos of the ancestors, since as far as the writer has been able to study this condition there is no human abnormality more persistent in perpetuating itself by inheritance. If, therefore, we do not understand the disease, we can also not understand its symptomatology which at times is extremely perplexing. It is not difficult to say, for instance, that the subjective symptoms are due to general neurasthenia and to atony of the digestive tract. What does the clinician mean when he says general neurasthenia? Has he any definite conception in his brain, which is capable of being met by an exact therapy? A few moments' reflection over this question will convince one how difficult the problem of symptomatology and treatment is.

At a recent meeting of the American Physiological Association (December, 1911), Meltzer and Joseph, as well as Cannon, reported on Experiments on the Effects of Stimulation of the Peripheral End of the Splanchnic Nerves. Meltzer and Joseph made use of the pupil as an index of the effect of stimulating the peripheral end of the splanchnic in augmenting the amount of adrenalin in the blood. They had extirpated the superior cervical ganglion prior to stimulating the splanchnic. This ganglion sends fibres that stimulate the constrictor muscles of the pupil, just the reverse of what suprarenal extract would do; therefore, this substance could show its effect only after antagonistic activity of this ganglion has been excluded in mammals. For a complete account of the effect of adrenalin on the viscera in general, the reader is referred to the writer's "Manual of Physiology," pp. 160-7.



Both Meltzer and Cannon have demonstrated that the stimulation of the peripheral end of the splanchnic causes an increased secretion of adrenalin into the blood, because this stimulation is followed by dilatation of the pupil.

The effects of adrenalin on various tissues are analogous to the effects of stimulating the sympathetic nerves which supply those same tissues. Prominent for our discussion are the following effects: (1) In all blood-vessels it causes constriction; (2) the pupil is dilated; (3) the muscle of the intestine in all mammalia is inhibited with the exception of the ileocecal sphincter; (4) the stomach in mammals is relaxed; (5) the effect of stimulation of the sympathetic nerves on the bladder and uterus varies in different animals, but a similar one is always produced by the application of adrenalin. Over twelve years ago Dreyer\* demonstrated that the secretory nerves of the adrenals are contained in the splanchnic.

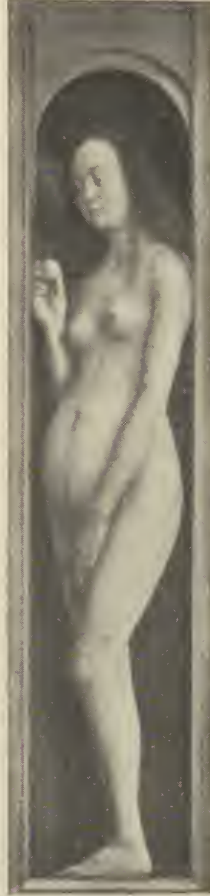
What bearing has all this physiology on the symptomatology of splanchnoptosis? It is a common experience of clinicians that the most far-reaching and poignant of all the subjective symptoms of the splanchnoptotic are referable to his sympathetic nervous system. It appears to be in a state of continual irritation, and this is explainable by the plausible assumption that the splanchnic nerves are in a state of more or less variable but continuous irritation, caused by traction on the abdominal ligaments by the displaced organs or by the weight and pressure of the organs themselves. In addition to that it has been assumed that the altered chemistry of digestion, that the writer has already referred to, produces altered products of proteid and carbohydrate decomposition, which in turn the diseased lining membrane of the stomach and intestine is incapable of resynthesizing during absorption. Bacterial decomposition also may play a rôle. At any rate, in any outspoken and pronounced case of the disease, the patient appears to be in a more or less permanent state of sympathetic irritation associated with gastrointestinal auto-intoxication.

*Splanchnoptosis without Symptoms.*—That there must be a gradual adaptation of the system brought about through generation after generation of splanchnoptosis is suggested by the fact that such cases are occasionally met with in the better walks of life where comparatively good health was enjoyed; and, moreover, even where there are symptoms during adolescence and middle age they disappear during advancing age. The danger of splanchnoptosis or constitutional visceral and vascular asthenia, therefore, becomes less and less as age progresses.

*Objective Symptoms.*—The most striking signs are revealed by mere inspection, for the abnormally elongated and narrow thorax, the long neck, the obliquely declivitous shoulders and the declivitous ribs at once portray the *habitus enteroptoticus*—the outward indication of a universal asthenia of the nervous system and the blood-vessels. Very likely the

\**Amer. Journ. of Phys.*, pp. 200-203, 1899.

latter are only secondarily affected through a lack of proper vascular tonus, which, as we know, is dependent upon an unceasing control of the blood-vessels by vasomotor nerves. The abdomen shows thin, flabby walls. It is stretched out and elongated. The distance of the navel from the xyphoid cartilage is shown in the writer's measurements to be much above the normal. The upper part of the abdomen may be flat or even con-



Reproduction of a classical painting by van Eyck representing Eve. Altar painting from the Cathedral at Ghent, Belgium. The figure is here reproduced to demonstrate that the model must have been a woman with the evident build of a case of splanchnoptosis.

cave, and the lower part arched outward, particularly on standing. This arching forward of the lower contours of the abdomen is produced by the weight of the displaced stomach and colon.

*Splanchnoptosis Cases Depicted in Classical Paintings.*—The models for the classical painters must have been individuals of the lower stations of life, for we frequently see in the paintings of the Italian and Holland

school representations of human beings who have the unmistakable objective signs of splanchnoptosis; and the most amazing thing about these classical paintings is that great artists took these disproportioned individuals for models to represent Adam and Eve. See for instance the painting Jan van Eyck on p. 9 of Dr. Eugen Holländer's beautiful work "Die Medizin in der Klassischen Malerei." The writer has measured the proportions of this woman's arm with a pair of accurate compasses and found them abnormal. Observe also the long sunken-in thorax and the protruding abdomen.

The Adam and Eve of Andrea Verocchio, of Hans Memling, and the female figures of Botticelli are examples of classic paintings taken from enteroptotic models. And in the paintings of Lucas Cranach individuals with pendulous abdomens are seen, which by art critics are assumed to represent pregnancies, but are surely taken from cases of splanchnoptosis.

Even some of the models of Rembrandt are apparently taken from splanchnoptosis cases. The infraxyphoid or epigastric angle is very narrow. Concerning the significance of the floating tenth rib, the writer has already drawn attention. It will be unnecessary to go into detail as to the methods used in ascertaining the size and location of the abdominal and thoracic organs.\*

*Prognosis.*—The hopes of clinicians, to cure such a condition as the writer has pictured in the foregoing, find their limitations in the fundamental constitutional abnormality, conditions which are congenital and which cannot be removed. The asthenic architecture of this class of individuals is persistent, and the anatomical deviations, which he has described as occurring in the viscera, are permanent. Splanchnoptosis must therefore be regarded as an irreparable condition. If some authors, for instance Einhorn, claim to have restored gastropotosis to a perfectly normal position,\*\* we must believe that it was not a case of genuine enteroptosis, but one of those types of pseudogastropotosis without the general constitutional asthenia that are usually described as "acquired." That such gastropotosis might be acquired, for instance, from tight-lacing, or loss of the tonus of the abdominal recti muscles, is quite intelligible; and the removal of the cause will bring about a restoration to the normal position.

*Treatment.*—It is the great desert of Glénard to have in his very first article on the subject called attention to the fact that these visceral displacements are always associated with a profound neurasthenia.† The entire literature of the subject up to the year 1910 is quoted in the writer's "Diseases of the Stomach." Although it is impossible to place the displaced organs back into their normal position, it is not difficult to treat

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\*Hemmeter: Diseases of the Stomach, pp. 693-730; and Diseases of the Intestines, Chapter on Enteroptosis, Vol. II, pp. 463-470.

\*\*Berl. klin. Wochenschr., 1896.

†Enteroptose et Neurasthénie, Soc. Méd. des Hôp. de Paris, 1886.

successfully the neurasthenia. The treatment of enteroptosis cannot be based upon causal indications, because the splanchnoptosis is congenital and persistent, and therefore all therapy must be directed to a general invigoration and improvement of the nutrition of the patient. If the writer should be asked to state the basic principle of treatment in enteroptosis, he would say avoid surgical operations, apply external supporting bandages carefully adapted to each individual, and fatten the patient. The treatment then should be (1) dietetic, (2) mechanical, and (3) medicinal. If the peristaltic power of the stomach is good, it is not wise to give a hard and fast dietetic schema. Let them eat almost anything they please except such food as is manifestly irrational. As long as the stools indicate that the food is digested well, the tyranny of a severe diet should be avoided. As soon, however, as the expulsive power of the stomach is impaired, the patient should then be put in bed, submit to a Mitchell-Playfair rest and fattening cure. The principle of the diet is the same as in atony of the stomach, small and frequent meals consisting of highly nutritious substances. The assimilation of proteid and fat will show itself by three evidences: (1) Better nerve reaction and resisting power; (2) improved condition of the cellular elements of the blood; and (3) increased strength of the patient as shown by the ergograph.

*Mechanical Treatment.*—It is not an easy matter to find a proper abdominal bandage for each case of splanchnoptosis. It requires personal and individual study to discover the proper fitting bandage for each case, for frequently patients are so lean that no bandage will fit well. Plaster bandages, such as are recommended by Lincoln,\* and also by Rosewater, are very helpful. They should always be put on with the patient in a reclining position.

*Medicinal Treatment.*—When colitis or gastritis occurs, it has to be treated just as this condition would be when no splanchnoptosis is present. Persistent obstipation is a very annoying complication. It calls for oil enema, a properly selected diet, and an occasional laxative of which aloes and phenolphthalein combined with strychnine are the least harmful. The writer must emphasize his repeated experience that the so-called purgative mineral waters, especially the Hunyadi-Janos and the Rubinat-condal, are actually harmful; in fact, all waters, the action of which depends upon a concentration of salts, are injurious. When there is much gaseous distension all carbohydrates should be eliminated from the diet. The magnesium salicylate sometimes gives relief in these cases of gaseous fermentation, but not if the diet contains the regular amount of carbohydrates. Electrical treatment by means of the slow, long-waved sinusoidal current applied with one plate over the spine and the other over the umbilicus, has, in a number of cases, appeared to me to improve the peristaltic power of the stomach and in-

\**Medical Record*, p. 69, January 12th, 1901.



testines. Whenever it is intended to treat the gastro-intestinal tract by electricity, it is well to bear in mind that it is moved by plain or involuntary muscle-fibre for which the electrical stimulus is not as adequate as it is for voluntary fibre. It is necessary to bear in mind that involuntary muscle-fibre requires a far greater current to affect contraction; and the rate of stimulation to produce a tetanus of unstripped involuntary muscle is much slower than for cross-striped muscle. For the stomach muscle, for instance, the best effects are obtained by one stimulus at each five seconds. This disregard for the peculiar reaction of unstripped muscle to electricity gave rise to an interesting controversy between Einhorn and Meltzer about twelve years ago, and which can be found recorded in Boas' *Archiv fuer Verdauungskrankheiten*. The principle reason why some clinicians get no effect from electrical treatment of the gastro-intestinal tract is to be found in this difficulty. They fail to adapt the kind, quality, and intensity of the electric current to the peculiar physiology of the plain muscle.

*Surgical Operations for Splanchnoptosis.*—In the writer's "Diseases of the Stomach" (p. 727) he expressed the hope at that time that it might become possible to treat this condition by surgical procedure. It was twelve years ago since that was first written, and he has kept a very close record of those cases upon which such surgical procedures were undertaken. In more than two-thirds of those from whom he could get a record, the stomach, when sewed into normal position in one way or the other, did not stay there, but was found displaced again in periods varying from one year to eighteen months after the operation. Reflecting again upon his conception of enteroptosis, the writer considers it his duty to emphasize that the surgeons that undertake such operations start from false premises; and it is his conviction that reports concerning the results that are claimed for such operations are based upon an insufficient period of observation, and are to be taken sceptically. Surgical treatment of enteroptosis, in my conviction, is only justifiable when the dislocation has secondarily led to complications; for instance, when a floating kidney has led to symptoms of incarceration in the ileocecal region, when the colon is so elongated as to have caused ileus, or when an extremely prolapsed stomach produces a kinking off of the duodenum. After having closely observed the after-effect of many abdominal operations in the hospital of the University of Maryland, the writer concluded that such complications are extremely rare. He also considers it his duty to publish the fact that in 3 cases the death of the patient was directly attributable to excessive surgical enterprise. Two of these cases were in wives of physicians, which he saw about one year before their death. A gynecologist had performed a double nephropexy, but in one case the right kidney was loose again, and in the other the right kidney was in the state of the fourth degree which has already been described in this paper. Another surgeon had operated for gall-stones on the same patient but found none.

A third had removed the appendix and both ovaries. Both these women had the scars of four extensive operations. Not one of these operations was justifiable in the writer's opinion; he insists on the fact that splachnoptosis is a persisting condition that is congenital and cannot be cured by surgical procedure. It is deplorable that these patients are so readily persuaded to be operated upon, and it is much more regrettable that the true nature of splachnoptosis is so little understood that there are always surgeons to be found who are ready to perform such operations.

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## TECHNICAL AND SCIENTIFIC QUALIFICATIONS OF A TEACHER OF PHYSIOLOGY

By JOHN C. HEMMETER,

*Member of the Deutsche Physiologische Gesellschaft; Professor of Physiology, University of Maryland.*

Our country was the only one in which it was legal to organize medical schools by an association of private individuals during the latter half of the last century. The result was an exuberance of so-called schools that were in reality stock companies organized by private practitioners with a view to benefiting either directly from the tuition fees or indirectly from consultation work brought by students and graduates.

As medicine became more and more an exact science by the growth of anatomy, physiology, chemistry, pathology, bacteriology, it became evident to even the egotistical managers of what might without exaggeration be called "Commercial Medical Schools" that certain subjects were beyond the ability of the "physicians" as then educated, and they were compelled *nolens volens* to elect specialists in chemistry—men who had obtained the degree of Doctor of Philosophy in one of our foremost endowed universities by a thorough and intensive study and research work in chemistry. This was a step forward, but physiology was still taught largely in a dilettantish, amateurish way by practitioners who had no special, or at best only a very superficial, training in physiology.

Chemistry is not a science that is based on many adjuvant or collateral branches of human knowledge—a preliminary A.B. in a good college apparently still equips a man to enter on this special study. But physiology demands of its devotees a thorough training in numerous other independent sciences. Chemistry is a structure of human knowledge self-sufficient in itself; perhaps physics may be considered as an adjuvant science indispensable to an understanding of chemistry. Physiology—the science of the regular processes that go on in living things—requires a preliminary

training in chemistry, physics, botany, general biology and anatomy.

To be a physiologist a teacher must make himself an expert in hundreds of little and major operations where the instrumental technique—the asepsis and the knowledge of anatomy—indicate whether a teacher is a dilettante or a trained experienced physiologist.

In addition, the science of life has in the last 20 or 25 years been so enormously extended, such a wealth of literature has accumulated and is constantly being added to, that unless a teacher speaks, reads and writes at least three modern languages it is almost impossible to keep abreast of the progress of his own time in the advances that are made.

Personally, I have found that my own course in physiology requires readjusting and remodeling every year, so that my system of physiologic discipline has not been alike in any two years, and it would be fatal to inculcate into the mind of any class of students that such a course could be so given that all lectures, demonstrations and conferences would be exactly alike in two consecutive years, for to them this would soon mean that the science had stood still, and that means stagnation. A teacher must never cease occupying himself with one research or another if he desires to be a true university teacher, for only as a research worker can he gain a deep insight into the whole biochemic and biophysic driving mechanism of the living substance.

Strange as it may seem, the absorbing interest and training in clinical medicine exceedingly rarely fits a man for the teaching of physiology, whereas a training of exhaustive thoroughness in physiology is the best preparation imaginable for the clinician. The reason for this divergent mutual utility between clinical medicine and physi-



ology is to be sought in the fact that only exact and objective sciences can be fundamental to other sciences. And medicine is not an exact science. But physiology is becoming one of the most exact and objective sciences that the human mind has formulated; it postulates absolute emancipation from the intuitive and imaginative functions of the mind and unconditional submission to the hard yoke of objective investigation. A kind of mind that is only exceptionally and exceedingly rarely developed by a medical training.

The period during which the medical faculty could appoint practitioners of medicine to fill the positions of teachers in physiology has passed 20 years ago. It is just as impossible for a practitioner of medicine to teach physiology as it is for him to satisfactorily fill the chair of chemistry. A highly-specialized physiologic technique has become indispensable, in addition to the thorough grounding in the facts, doctrines and hypotheses of the science itself, and to have physiology taught by one who by habit is accustomed to thinking only clinically gives physiologic science a twist and warp in the hands of such a man which distorts its aim and makes true understanding of the normal processes of life practically impossible. From *Old Maryland* for May, 1907, p. 66, we quote the following: "In order to have physiology taught in the highest and most skilful manner, Dr. and Mrs. J. C. Hemmeter have made an agreement with the trustees of the Endowment Fund of the University of Maryland, which was made in 1907. The following extract is taken from this agreement as it appeared in *Old Maryland* for May, 1907, p. 66:

"In beginning an Endowment for a Chair of Physiology in the University of Maryland, Prof. and Mrs. John C. Hemmeter 'recommend and request' that the Board of Trustees observe the following conditions: 'The first installment of \$1500, together with future yearly contributions and such legacies as will be bequeathed for this same purpose, are to be kept at interest until the principal has accumulated sufficiently to yield a salary of at least \$3000 annually to the professor holding the chair at the time when this amount shall have accumulated.

"If at that period a larger salary is required for a professor, the \$3000 annually accumulating from this fund may nevertheless be utilized for this purpose, provided the administrative body of the University of Maryland at that time agrees to

supply the difference needed to complete the amount required.

"It is urgently desired that the benefits accruing from this fund shall not be available or granted to any teacher who is not a *trained physiologist*. By that we mean that he must have made a special study of physiology for at least four years in the laboratories of physiology of one or other of our larger universities, such as Harvard, Yale or Columbia of the City of New York.

"We distinctly desire to have it understood that the benefits from this fund are not to be granted to teachers who simply have a degree in medicine only, and have no special training in physiology. What we understand by special training is defined in the preceding. The object of this is to make the teaching of physiology more and more objective, and not to depend upon lectures exclusively, but more upon laboratory work.

"In awarding the professorship it is our desire that candidates who are born and educated in this State, and particularly alumni of this University, shall be given the preference; but if none such can be found who have gone through special training either in Europe or in the large universities of this country, candidates from any State or nationality may be selected."

"The founders of this fund do not state the amount it is their intention to give to it, but declare that provision will be made in their wills for its increase. The fund now amounts to \$5400." The founders of this fund should insist upon the conditions of high and exclusive scholarship, technical training and ability, together with a broad experience. For broad experience, conservative yet penetrating critical judgment, a fanatical enthusiasm for truth and exactness, together with a warm, sane heart, are qualifications *sine qua non* in physiologic discipline. The thought may occur why medical men are to be excluded from the chair of physiology, since the writer is himself a clinician. It is because of this very fact that he is best able to realize his own shortcomings as a teacher of physiology, and that as far as the University of Maryland is concerned, the list of clinician physiologists will end when his activity in that chair ends. His successor will be a trained physiologist pure and simple, and the days of the last Medical Mohican in that science are come when he terminates his connection with this University.

## A FRIENDLY CONTROVERSY BETWEEN TWO PHYSIOLOGISTS CONCERNING THE MECHANISM OF THE LESSER CIRCULATION (RETURN OF BLOOD FROM THE GILLS TO THE SINUS VENOSUS) IN ELASMOBRANCH FISHES

By JOHN C. HEMMETER, M.D., Phil.D., LL.D.,  
*Professor of Physiology, University of Maryland, Baltimore, Md.*

In the *Zeitschrift für Biologische Technik und Methodik*, Bd. 2, p. 236, November, 1911, I published an explanation of the forces that bring the blood back from the gills to the sinus venosus in the heart of the *selachii*. This heart consists of sinus venosus, which is the first part of the heart located in the pericardium toward the caudal end; this empties into the single auricle, and this into the powerful ventricle. The ventricle sends its blood through the bulbus arteriosus and aorta to the gills.

Whilst the blood pressure in large specimens of dogfish, for instance, may be very considerable in the ventral aorta going to the gills, the vessels returning the blood from the gills show no positive pressure whatever, and we did not succeed in measuring whether there was any negative pressure with the instruments at our disposal at the Woods Hole laboratory during the summer of 1911. In three vigorous specimens of *mustelus canis* the pressure in the ventral aorta was 88, 92 and 96 mm. of mercury, respectively, but after the blood had been passed through the fine capillary network of the gills and re-collected again it shows no positive pressure whatever; but there is some slight evidence that the blood appears to be sucked caudad toward the sinus venosus. What causes this force to bring back the blood from the gills to the heart?

The influence of the respiratory motions of the fish in favoring the return of blood to the sinus venosus has been described by me on page 238 of the above article.

But during a great many experiments I noticed that the pericardium was a very tough bag, and that it did not collapse to any noticeable degree

when the ventricle contracted, but was about the same size during the systole and during the diastole of the ventricle. The ventricle is the strongest and most muscular part of the heart. When it contracts it becomes very much reduced in size, but as the pericardial sac does not become smaller during the ventricular systole, the thin-walled sinus venosus and auricle are sucked into the space vacated by the ventricle. In other words, there is a slight negative pressure created in the pericardium when the *auricle* and *ventricle* contract, and this is filled by the aspirating into this new space of the sinus venosus. This negative pressure is sufficient to fill the sinus venosus from the sinus of Cuvier. At times the respiratory muscles of the fish which draw the water into the mouth and out through the gill slits, contract simultaneously with the ventricle. Now, in some of these fishes the respiratory muscles (coraco branchial) exert a traction upon the pericardium, thus, as the ventricle gets smaller in size, creating a negative pressure in the pericardium, this sac, far from collapsing and following the ventricle, is pulled in the opposite direction by the outside traction of the respiratory muscles.

In the elasmobranch fishes there is an open canal which connects the pericardium with the peritoneum, known as the pleuro-peritoneal canal (pericardio-peritoneal canal would be a more correct designation), which drains the pericardium toward the peritoneum; owing to valves in this canal, however, no fluid can enter from the peritoneum into the pericardium. Therefore, a *negative pressure* is possible in the pericardium, but not a *positive pressure*, for if a positive pressure were ever created in any conceivable manner

it would be spent toward the peritoneum through this canal. Delicate water manometers tied into the abdominal side of this canal indicate always a slight negative pressure with each systole of the ventricle; never a positive pressure.

So the explanation I offered was that the return of blood toward the sinus venosus from the gills was due to a negative pressure in the pericardium caused in the manner described. When I explained this mechanism to my friend, Prof. G. H. Parker, who was working in the same laboratory (that of the United States Fish Commission at Woods Hole, Mass.), he informed me that this discovery had already been made by Léon Fredericq at Liège, and in the article written by me I credited Fredericq with having first explained the respiratory circulation in the fish and the return of blood to the heart in this manner. On the 8th of February, 1912, I received the following letter from Professor Fredericq:

"Most Honored Colleague—I have read in a very interesting article by you ('Methodik der Gleichzeitigen Registrierung des Atmungs- und Herzrhythmus beim Selachier') in the *Zeitschrift für Biologische Technik und Methodik*, November, 1911, p. 236, a description of a method concerning the return of blood from the gills to the sinus venosus in the fish which you credit to me. You will oblige me very much by indicating where you have found this method described, as I cannot recall having published anything concerning this subject. In expressing my thanks in advance, will you please accept the assurance of my most cordial sentiment?

"LÉON FREDERICQ.

"P. S.—You may reply in English or German, just as you prefer."

Thereupon I communicated again with Professor Parker, who sent me the following letter:

"Dear Dr. Hemmeter—The idea I had about the return of blood to the heart of a fish applied to those cases where, as in the skate, the walls of the pericardium are firm. My notion was that the contraction of the ventricle in a firm-walled chamber would of necessity cause the auricle to fill by sucking in blood from the venous sinus, etc. Such a condition would imply a negative pressure in the blood cavities immediately behind the heart. I remember talking this over with Dr. Willem at Naples, and he told me that this negative pressure had been demonstrated by Léon

Fredericq at Liège for certain fishes. This conversation was in 1893, and the whole affair is naturally somewhat hazy to me now, but I believe I never knew whether these observations of Fredericq's were published or not. I am sorry I can't send you more satisfactory information.

"Spaeth and I have just completed a hard half-year's work, and we are beginning to feel more ourselves again. With kind regards to Mrs. Hemmeter, I am,

"Very truly yours,

"G. H. PARKER.

"Zoological Laboratory, Harvard University,

"Cambridge, Mass., February 13, 1912."

On receipt of this letter from my friend, Dr. Parker, I sent the following communication to Professor Fredericq:

"Baltimore, February 15, 1912.

"M. le Professeur Léon Fredericq:

"My Dear Colleague and Honored Friend—From the error I have made in my article on 'Methodik der Gleichzeitig. Registrierung,' etc., in the *Zeitschr. f. Biologic. Technik.*, Hft. 5, Bd. 2, November, 1911, p. 236, attributing to yourself a physiologic contribution which you say that you have never published, you will recognize one of the embarrassing accompaniments of your greatness, for discoveries are credited to you which you have never made.

"On the other hand, the error shows what undesirable complications we may be led into by overconfidence in our friends whom we know as great authorities. Inclosed I hand you a letter from my friend, Prof. G. H. Parker, professor of zoology at Harvard University, Cambridge, Mass.

"Parker worked in the Marine Biological Laboratory at Woods Hole, Mass., all of last summer, and I asked him about this very physiologic question concerning the return of blood from the gills to the heart in fishes, and he gave me to understand that you had done this work. Knowing Parker to be one of the greatest zoologists of our country and a very thorough and broadly-educated man, I did not doubt his statement, nor did I take the trouble to look up any reference on the subject.

"As I was teaching your contributions to respiration to my students every year, it seemed so natural and self-evident that you should also have made this discovery on fishes. If you desire



me to correct this error, I will send a letter to that effect to Prof. Martin Gildemeister, the editor of the above *Zeitschrift*.

"I may add that this mechanism of the negative pressure created in the pericardium of the elasmobranch during the contraction of the auricle and ventricle was worked out by me at Woods Hole last summer, and I did not claim it as an original piece of work, because Parker stated that you had already made this discovery. As you now disclaim ever having done such work, it will be best for me to publish my experiments on this subject.

By invitation of Prof. H. J. Hamburger I hope to be in Groningen next fall to attend the meeting of the International Physiologic Society. Perhaps I will have the pleasure of seeing you and meeting you there.

"My new work, 'Manual of Physiology,' was published this week in Philadelphia. Can you tell me the exact date of the meeting of physiologists in Groningen?

"Hoping you are well, and with kindest regards, I am,

"Yours very sincerely,

"J. C. HEMMETER.

"739 University Parkway,

"Roland Park, Baltimore."

On March 10, 1912, I received the following reply from Professor Fredericq:

"Institute of Physiology, University of Liège,

"February 29, 1912.

"My Dear Colleague Hemmeter—Thank you for your kind letter. Herewith I return Professor Parker's letter. I cannot imagine how Dr.

Willem could have made the mistake of attributing to me merits which I do not possess. Indeed, I have never undertaken any work on the circulation of bony fish. With regard to elasmobranch fish, I limited myself to the collection of blood, but never made any experiments in the circulatory mechanism.

"It does not seem worth while to trouble you with writing a correcting article. You will certainly have the opportunity of some day correcting this point, which is of no importance to me in your future publications.

"I am glad of the opportunity which brought us in contact with each other, and hope to have the pleasure of meeting you in Groningen in 1913.

"Your friend, Professor Hamburger, has been to see me at Liège last week. He told me of your splendid work and that the congress opens its first Tuesday in October, 1913.

"Yours very devotedly,

"LÉON FREDERICQ."

I publish this correspondence not simply because it authorizes me to publish under my own name an important contribution to the comparative physiology of the circulation, but, what I esteem far higher, it gives evidence of the high-minded manner in which men with warm, sane hearts adjust their differences. Too frequently we see men who claim extraordinary mental culture attack their confrères in a disingenuous manner calculated to injure their good name and self-respect.

The correspondence with Professor Fredericq illustrates how leaders of thought in natural science, if they are true lovers of science, will naturally observe the "Golden Rule."





*Reprinted from the New York Medical Journal for  
December 7, 1912.*

TENDENCIES OF MODERN PHYSIOLOGI-  
CAL DISCIPLINE IN MEDICAL  
SCHOOLS.\*

*Principles and Objects of Physiological Discipline.*

BY JOHN C. HEMMETER, M. D.,  
Baltimore.

The development and growth of physiology in the last twenty-five years has been so great, that even the best trained mind of the technical physiologist finds it difficult to keep abreast of the progress that has been, and is still being made. It is all the more astonishing, therefore, that in medical schools in which the councils of men prevail who have only an exclusive medical training, one still meets with the idea that physiology could be taught by men who are not trained physiologists, but by practitioners of medicine who obtained their knowledge at second hand from textbooks only, and have no personal experience with research work, nor even an intimate control of the truths, doctrines, and theories of modern physiology.

With regard to chemistry, even the orthodox medical mind has long ago abandoned this idea, and in even the poorest medical schools, chemistry is taught by a technically trained chemist, and pathology usually by a trained pathologist. It is for the purpose of clearing up this erroneous opinion that this article was written. It was first discussed with a number of eminent physiologists in this country and abroad and many of the ideas were received from Jacques Loeb in an almost daily intercourse at Woods Hole, Massachusetts, during the summer of 1911, but also from other experienced teachers in

\*Address delivered at opening of the course in physiology at the University of Maryland, October 1, 1912.

physiology who were engaged at the Woods Hole Marine Laboratory. The article by Verworn entitled, *Aufgaben des physiologischen Unterrichts* has inspired some of the main arguments. I am also indebted to Professor J. P. Pavloff, of St. Petersburg, for much inspiration toward this article, gained as well from his writings as from a private correspondence with this great physiologist and brilliant scholar.

Some of the principal thoughts I have quoted from the preface to my *Manual of Physiology* (Philadelphia), the principal one of which is contained in the remark on page 10 of the preface. There are systems of economics of intellect and in physiological pedagogy and physiological discipline they demand no cast-iron rigid scheme, but elastic fundamental concepts—lifelike, plastic aspects, not a mass of disconnected single knowledge. Only that which is assimilated, of and by itself continues to live and work in the intellect.

In the following I shall endeavor also to give the reason why the secret of success in the future teaching of physiology is to be found to a large extent in general and comparative physiology.

Physiology is, at the present day, not a finished science with subject matter established and immovable in every particular in the same sense as in her sister science, descriptive anatomy. In this respect the anatomist is far more happily placed. So far as the descriptive anatomy of man is concerned, at least, the structure of the science is, in a manner, finished. The subject matter for academic instruction is outlined within certain circumscribed boundaries. Hence the lectures on anatomy delivered in the various universities agree in the main. Not so in physiology. True, there is also a vast area of facts in physiology that can be considered established, and which must self evidently form the basis for all physiological instruction. But then facts are interrelated in a very loose and merely superficial

manner, and frequently stand dissociated and alone. The science of physiology is still very much in a state of development.

On the other hand no biological discipline makes as many demands on its votary. The number of auxiliary sciences is so great, the methods of investigation are so complicated, the problems so difficult, the subject matter so delicate, that it can easily be understood why investigators confine themselves to one or but few of its many special branches. It is no longer possible for an investigator to engage with searching thoroughness in all the departments of physiology as was the case in the days of Johannes Müller, before physiological investigation and method assumed the present proportions. To-day physiologists become conversant, one in the physiology of digestion and the metabolism change of living matter, or of electrophysiology, another in that of the central nervous system; one confines himself almost exclusively to the chemical composition of certain forms of animal matter, another to the mechanical principles underlying circulation; one to experiments on change of matter, another to the physiology of the organs of perception; some, again, to the physiology of the enzymes. This onesidedness in investigation, which cannot be avoided with the natural limitations of human life, and necessary in a measure if research work is not to drop to a dead level, brings with it a certain differentiation in physiological instruction according as the topics are considered highly important or insignificant with the time limitations of the academic course.

Thus it happens that some one attending physiological lectures at two extremely diverging universities, would almost receive the impression that he is taking courses in two different sciences and, all the more so, if the methods of instruction are at variance (Verworn).

It now behooves us to explain the importance of physiology in the training of a physician. Physiol-



ogy is the science of life or of the biological phenomena in organisms or, as has been said, of the chemical transactions in or functions of the organism and its parts. In this vast field of general physiology, the special physiology of the human body is of prime importance to the future physician. The fundamental importance of this branch of physiology in the study of medicine has never been questioned. The physiology of man, together with human anatomy, constitutes the indispensable basis on which the structure of medical science and skill has been reared since the days of Galen and this will ever be so. Without physiology there will be no practice of medicine. Physiology is to picture clearly the biological activities in the normal body, the part the several organs in the human body play in the activity of life under normal conditions, so that at any given moment an account can be rendered of what is actually going on in the human body. The more plastic and accurate the picture, the more clearly possible this visualization of the activities in the body and its parts under normal conditions, the more profitable it will be to the physician at the bedside, for sickness is nothing but life under difficult conditions.

But how can the abnormal be recognized and understood when the normal is not sufficiently known? How could a physician restore to health, that is, correct the course of abnormal digestion, if he did not know these biological functions in a sound body? The more thoroughly grounded in physiology, the better a physician. The reverse may also be stated as true, that the brilliant physiologists in the history of the science have been such as were also physicians. But the training in clinical medicine alone does not fit one for the teaching of physiology as well as the training in the latter fits one for the pursuit of clinical medicine (see Hemmeter, *The Technical and Scientific Qualifications of a Teacher of Physiology*, in *University Hospital Bulletin*, Baltimore, May, 1912).

It is not inordinate to point to the dangers into which lack of physiological knowledge can draw the science and practice of medicine, and into which it has been led by various pilots in the present day. It is unnecessary to say that physicians do make mistakes at the bedside for which they must pay the penalty, mistakes that could easily have been avoided with a fair knowledge of physiological processes, but it would be well to glance at two great blights that are exceedingly annoying to the medical profession at the present time.

Much has been said recently about quackery and of the struggle of physicians against it. Few are perhaps correctly informed on the enormous spread of quackery and that, too, in an age that points with pride to its general culture. In what alarming a light this reveals the true status of the education and discriminating ability of the general public! The consideration of this question ought to be taken seriously to heart; unpleasant contact with it is inevitable in the practice of medicine. The whole matter would be comparatively harmless if it were confined to barbers and teachers and patent medicine men, or people of like professional training, as it was in olden days. The doings of men of that stamp could be witnessed with indifference; for those who surrender consciously to their treatment would only have themselves to blame and, although generally too late, they would eventually fall into some physician's hands.

But the situation has become far more ominous to-day. Persons decorated with the title of doctor of medicine are not abashed to practise quackery much after the manner of the charlatans and wonder doctors of the sixteenth and seventeenth centuries, who meandered from pillar to post in their carts and in fanciful garb, with tinkling bells, lauded their remedies before the multitudes of those alarmed at their ailments. Whenever a man on whom a medical faculty has bestowed the title of doctor practises medicine under such guise, the pub-

lic cannot escape being shamefully deceived. Such conditions are admissible only where the foundations of medical science are lacking. A man who is reasonably acquainted with the biological activities in the body, and who has gained but one clear glimpse into the physiological happenings in the organism, could never lower himself to the fallacious practice of quackery unless he did so against his better judgment and from base motives.

Another danger to which the physician is exposed in consequence of inadequate ideas about the nature of biological phenomena and the physiological processes in the organism, lies in the total misconception of the physiological significance and the therapeutic value of many modern specifics. On this score practice has made many blunders in recent times. When the untutored patient demands of his physician as large a bottle as possible of intensively colored bitter medicine for every trifling ailment, this is excusable on the ground that the quaint ideas on the healing of the sick of bygone centuries yield reluctantly to better insight in the public mind. Hence, the physician is often obliged to prescribe for no other reason than to be doing something. But when, instead of treating diseases along the line of insight into their causes, the processes of the organism, and in harmony with physiological demands, the physician simply seizes a chemical of doubtful value and but recently thrust on the market with a big "send off" by some chemical concern, he becomes guilty, rigorously speaking, of malpractice committed from a viewpoint of convenience: for what does he or any one else know of the physiological effects of the preparation in question?

The danger would, however, not be very great, if the state of modern trade in scientific pharmacology were not in the most deplorable condition imaginable. Instead of originating solely in medical research and science, as formerly, modern scientific pharmacology is overshadowed by the product of manufacturers of chemicals. A large number of

the scientific representatives of pharmacology devotes itself, not to minute investigations on the physiological effects of remedial substances, but principally to the purely chemical questions on the constitution and chemical structure of substances contained in the animal body, or to experiments on metabolism. The pharmacologists are frequently only physiological chemists. In the meantime the chemical factories are producing multitudinous quantities of "new specific."

Experiments after the same general scheme are conducted on the effect of the most varied chemical combinations, and as is often the case, in the most slipshod and superficial manner. It is usually the same procedure in each case. A chemical is injected into a rabbit and then blood pressure and respiration are graphically noted. If a change occurs in these external manifestations, the substance can pass as a remedy. Then the dosing of human beings is tested in amounts that can do no very serious damage, the article is manufactured in large quantities, is dubbed with a beautiful name, and in a short time floods the market with the highest recommendations only to disappear entirely within a few years. In the meantime hundreds of new remedies have been discovered in the same way, with therapeutic effects equally eminent.

The short time which the enormous production of pharmacological products allows for the physiological testing of the separate articles, naturally precludes establishing what their effects are in the animal body and locating their points of attack. The bare investigation into their influence on heart action, on blood pressure and respiration throws no light on these questions. Every physiologist will scoff at this manner of examining a remedial substance, for the heart action, blood pressure, and breathing are purely external resultants of a large number of quite different and individual factors. Even after it is known that a substance influences blood pressure, next to nothing is known of its spe-



cific effect on, and its point of attack in the body. The same thing obtains concerning the influence on numerous other purely external physiological phenomena.

It is evident, therefore, how matters stand on the great abundance of "specifics of to-day" that rise like meteors in the pharmacological heavens. It is advisable, therefore, to be sparing in the use of drugs and to adhere closely to the few thoroughly tried and approved preparations whose physiological effects are already known with some degree of precision.

From the foregoing it is evident how urgent to the physician is the need of a clear, comprehensive view of the physiological occurrences in the human body. The deeper the insight into these matters, the more nearly correctly will the physician be able to pass judgment on diseases and their causes, the more purposefully will he choose his course of treatment, and the more successful will be his practice.

It is a great mistake, common in the practice of medicine, to place treatment by drugs in the foreground of therapeutics. The physiological factors in the art of healing have for a long time retreated too far behind the use of remedies. A practical physician, who has a vivid picture of the biological activities in the human body and of their more subtle causes, will not neglect the natural, purely physiological factors for the pharmacological.

Man is the most interesting and eminent subject of all science, for there will never be any subject that more immediately and more closely concerns man than man himself. This last must swell the heart of every medical student with pride in his profession, since man is the exclusive object of his whole activity. The physician ought to be the best judge of human nature. The physiology of man, therefore, represents for him the most important part of general physiology, not only in its general human, but also in its specific scientific aspect.

But the physiology of man is extremely comprehensive, and unfortunately here, as everywhere, "art is long and time is fleeting." With due regard for the many demands and the short time allowed to physiology in the study of medicine, a selection of the most important topics must be made from the vast area of human physiology. The most important object of this teaching appears to be, not to present a great mass of isolated facts collected from every chapter of human physiology, but rather to avoid disconnected subject matter, the memorizing of which can be mechanically acquired from books, but rather, to emphasize this point again, to give a plastic picture, a profound understanding of all the activities in the human body, a unified complex of fundamental concepts around which, as it were, the special facts as they present themselves are gradually to crystallize by themselves, i. e., of their own accord. Only that which is spontaneously assimilated, lives and toils and labors on in the mind. Isolated facts without organic connection, artificially and laboriously acquired, constitute dead knowledge to remain worthless and soon to be lost by the wayside. Fundamental objective visualizing, live concepts, not a profusion of disconnected isolated facts, is what is needed in economical mental housekeeping.

From this point of view special stress is to be laid on a part of universal physiology that has very slowly, but in the course of time, increasingly tended to crystallize out from the specialized researches in physiology as a precious gem, that is, *general physiology*.

The general physiological concepts which contain all the properties and laws common to all living bodies, furnish, in a certain sense, the key to all the doors behind which the numerous special facts concerning normal life lie hid. Without this master key only the outside doorplate comes into view, but the nature of the facts that slumber behind remains unknown, and the

separate facts cannot be called to life to be united into organic complexes. In the absence of summary knowledge of the facts of general physiology, the special physiology of man gains no profound understanding; without it the most beautiful attainments in this field remain lifeless. The physician, however, who has enjoyed a thorough training in general physiology, sees deeper down into the organism, before his mind's eye he visualizes the processes in the diseased cells, he beholds the causes of their changed conditions, and he will be better able to remove these causes. The less the healing art has general physiological visualizations at command, the lower it sinks into barren and tiresome schematization.

Among the chapters of general physiology of special importance to the physician, beside the knowledge of general biological phenomena, are what lie at the foundation of these, the cellular processes, above all experiences on the general hypotheses of life, and with special emphasis the laws of irritability. These chapters are of preeminent interest to the physician, since diseases represent nothing but the consequences and the external expression of changed conditions of life, or in other words, the deviations from normal biological phenomena in the cellular constituents of the body, induced by irritations. Hence it is of extraordinary importance for the physician to be acquainted with the biological phenomena in the cells under normal conditions, on the one hand, on the other hand, to know what deviations from the normal life are superinduced in them by irritants according to their quality, intensity, and direction.

The cellular pathology of Dr. Rudolph Virchow, on which all medical conceptions rest, and which must ultimately form the starting point, and basis even, for all effects in this direction of the modern pathology of tumors, assumes cellular physiology as a premise and can only grow extensively as the knowledge of the normal cell processes and the law-

fulness of the effects of the various irritations expands.

In consequence of a sufficient number of general physiological visualizations, the special facts of the physiology of man will appear in quite a different light. The life proceedings in the human body will be regarded from a higher level, with broader view, closer connections, and relations will be discovered everywhere, where, otherwise, only isolated disconnected facts presented themselves. This is absolutely necessary with the vast amount and extensive scope of subject matter. The several departments of physiology have assumed such proportions that some of them have moved out of touch with one another and have developed into individual sciences. Thus the science of embryology and morphology, which ought to form an integral part of physiology as it formerly did, has been divorced completely from modern physiology at a serious loss to both physiology and embryology, for from both vanished, at the same time with this separation, also the mutual understanding of their several problems and sympathy for their way of thinking.

Embryology is no longer lectured on in physiological courses. There is at least one justification here for the separation into a special branch. Embryology has its own special problems, that have proved so immensely manysided in the last decades and have called into existence an amount of scientific work so copious as to make even a survey well nigh impossible.

Quite different is the case of physiological chemistry, which is another department of human physiology, and which has also striven to gain a certain independence. Physiological chemistry has made special effort to branch off as an independent science under the influence of Hoppe-Seyler. The independence of physiological chemistry from physiology cannot be justified. Physiological chemistry has the same general aim as physiology, that is, the investigation of biological phenomena. This aim



physiology pursues with methods varied according to the demands of every special question. In its investigations physiology must apply physical and chemical, surgical and microscopical methods, according to the exigencies of the case. The fact that, with so many demands, each investigator selects some special field which he elaborates according to his special methods, is both tangible and justifiable.

The representative phases of the science vary considerably in the different universities, but physiology on the whole is rescued from narrowing monotony. But to institute a separate science on the ground of special methods, such as physiological chemistry, is entirely erroneous. A science is founded on a problem, not on a method; in the latter case inherent justification is wanting. If this proviso be lost sight of, then physiological physics, physiological surgery, and physiological microscopy could segregate themselves as independent sciences with the same justification as physiological chemistry. This would lead to hair splitting dismemberment of physiology into specialties that would soon have no common ground of interpretation, and would overlook the one and only aim and purpose in physiological investigations, the study of life.

Physiological chemistry has already confined itself in the main to but few special problems. The two foremost propositions in physiological chemistry are investigations on the composition of albuminoids and experiments on the changes of matter in dogs and rabbits; the former, together with the study of hydrocarbons, have been and will be, the work of pure chemistry, the latter must be reincorporated into the programme of physiology where it belongs (Verworn).

Specializing into even more specialized departments has already been carried to such a degree of nicety as to lead to embarrassing conditions. Physiology is, and must remain an undivided science. The application of the methods of chemistry is a part of physiology as is the application of any other

method, and academic instruction in physiology ought, correspondingly, to be one and undivided, and not be separated into courses on physiology and on physiological chemistry, each conducted independently by distinct lectures. Such a division of physiological instruction would lead to utter mangling for the student of the more special chapters of physiology, for there is no chapter in the whole of physiology in which chemistry does not play an important part, or which could be discussed without entering upon chemical questions. The student would be unable to get a useful survey of the subject as a whole.

Pursuing division on principle would also seriously embarrass investigation. If each instructor is to adhere closely to his own department it will give rise to neglect or abandonment of the other departments. The difficulties attending physiological investigations preclude the possibility for every physiologist to engage in individual research work on chemical problems, and likewise for him, whose dominant interests are chemical, questions of physics and microscopy are precluded. Each specialist is obliged to work with the best methods at his command. The lecture course on physiology offers the only clearing house where the physiologist can preserve a unified survey of the subject as a whole if he is forced to take notice of the problems, methods, and results outside his own province. Without this opportunity and this injunction there would still be physiological chemists, physicists, etc., but ultimately no physiologists; thereafter the general survey and with this a liberal and unconstrained grasp of the problem would be utterly lost.

The preparatory study of pure chemistry should be in the hands of chemists, that of physics conducted by physicists. Instruction in physiology as a whole will then contain elements in chemistry, physics, anatomy, histology, zoology, and botany. The one aim, however, to be pursued in all physiological instruction should be to give a comprehen-

sive unified picture of what is going on in the human body. In this sense the several chapters of physiology will be taken up in a certain sequence, issuing without constraint from the very nature of the subject.

The discipline is best begun with the fundamental principles of general physiology. At first these manifestations of energy, which are connected with transubstantiation in the body will be considered, such as heat, motion, evolution of electricity, the processes in the nervous system, and the functions of the organs of sense. This will be followed by a discussion of the entire change of matter in the human body, pursuing the fate of the alimentary substances to their excretion as waste matters; the properties of food, secretion, digestion, absorption, breathing, the composition of the blood and of the lymph, circulation, the changes of tissue, formation and excretion of the urine. It will thus be seen that the functions of one member articulate with those of another, and how they keep the clock-work of the human body going in unison.

The several special departments of the physiology of man vary in educational value for the physician. With the time limitations imposed upon physiological instruction, a retrenchment of the department of minor import will be necessary. In this respect the physiological instruction of the future will have to take on shape different from that of the latter half of the past century. Thus, it would not be admissible to allow as much time to electrophysiology as formerly. The phenomena, in view of the development of electrochemistry, have lost much of their theoretic interest for the biologist, and have become almost worthless to the physician who is concerned with such a picture of the biological processes in the body as can be of practical service to him. With all the inherent theoretical interest in the physiology of the muscles, it will be practical to devote less time to them than formerly, when it often embraced the main part of the lecture course

of a whole semester. This was formerly justifiable in a way because the general physiology of the muscles and neurology then constituted that part of physiology in which the physician became last acquainted with a general idea of physiology. Now that the conceptions, doctrines, and theories of general physiology have been segregated from the various departments of special research, and have developed into a comprehensive complex; now that physiology forms a separate department of physiology in general (collective physiology) and is treated as such in teaching, a minute treatise on the general physiology of the muscles is no longer offered in an academic course of medicine. The time thus gained is to be employed in other departments of physiology such as a treatise on the change of matter, and the physiology of the nervous system.

The amount of instruction in physiology of muscle and nerve has been indicated in my *Manual of Practical Physiology*. Looked upon from the extreme utilitarian standpoint it still constitutes a valuable preliminary training for the neurological clinic.

An exceedingly difficult question on the choice of subject matter in physiological instruction still remains to be answered: Shall physiology consider psychological questions and to what extent? Johannes Müller defended the thesis: *A physiologist nothing but a physiologist*. There is a great deal to be said on this question and it cannot be disposed of in a few words. It might be well for everyone engaged on biological problems to consider casually the question of the relation of material to psychic life, the question of the relation of body to soul, as it is called in current dualistic expression; for this question confronts us at every turn in biology. It plays into all possible contingencies and causes obscurity and confusion. Every biologist ought to come to terms on this question, and this can be done only by entering upon a critique of the understanding and especially upon the problem, what understanding is, and what its limitations are? No nat-



uralist can get around this, the supreme question in science, unless he is willing to surrender needlessly to blind specialism.

But whatever the answers to these queries, complete elimination of psychological elements from physiology and from physiological instruction is practically impossible. The chapters on the central nervous system and on the organs of perception cannot yet be discussed without psychological concepts, such as sensations, conceptions, consciousness, etc., otherwise than to render their presentation unintelligible. Besides, the later lectures on psychiatry will engage psychological considerations abundantly. Hence it is impossible to avoid entering upon psychological questions in physiological instruction, even if it were desirable to do so, and hence it will be advisable to take a firm stand and gain some clearness right in the start.

In consideration of the great complexity of the subject of physiology, and the difficult methods of approach in gaining insight and knowledge, it is necessary and all the more so in the lectures that instruction be as objective as possible. This is to be accomplished in two ways.

On the one hand the content will be presented in a simple plastic, living style. The utmost attainable clearness and simplicity are emphatically aimed at. Burdening the memory with numbers, tables, and formulas that are difficult to master and do not stick, will be avoided as much as possible. True, numbers and tables will not be withheld, but shall be offered only to illustrate certain facts. The student is to extract facts and ideas and to have at his command visualized pictures, not tables and numbers that can be obtained from any reference book when needed. An error into which physiological instruction easily falls is—too detailed entering upon the presentation of the more complicated methods and the arrangement of apparatus and experiments in special lines of research work. Surely, for better understanding, the student ought

to be informed as to the ways and means of arriving at certain physiological experiences. But this end is fully reached if the principle of the method or of the apparatus is sketched in the most primitive outline. Exact knowledge of every minute detail, on the contrary, complicates understanding, burdens the memory, and serves to no after purpose. These items belong to physiological research work, but not to physiological instruction. In either case it must not be forgotten that the live subject in hand is to stand in the foreground. Method is only means to an end. (Hemmeter, *Manual of Practical Physiology*.)

On the other hand, it is a function of physiological instruction to give a thorough knowledge of the more common and simpler methods which physicians must make constant use of. An acquaintance with certain chemical, optical, microscopic, electric, and surgical methods is indispensable for special medical purposes.

Other important factors toward attaining visualization of the subject matter of the lecture, are demonstrations and experiments. The most beautiful and clear presentation cannot be a substitute for that which has been "eyewitnessed," provided it has been understood. The lecture should be aided and supported as much as possible by demonstration on its subjects; but too intricate and unsurveyable experimental appliances and arrangements should be avoided, since these, according to experience, do not help understanding and often only perplex and subvert it. Clearness, perspicuity, comprehensibility, these must be the shibboleth of physiological instruction. Where the experimental contrivance or the apparatus is too complicated or inconspicuous, it will be far better to supplant it with a single schematic sketch on the blackboard or by a correspondingly simple figure on a chart. This device, and above all the drawing of objects on the board during the lecture, ought to find liberal application; for, on the one hand, the instructor can

omit what is subordinate, or what would impede understanding, and, on the other hand, the audience sees the object gradually developing before it, so that, in following the drawing, the demonstration becomes intelligible, whereas, if confronted with the finished drawing, the latter would be quite unintelligible. It is my own practice to draw on the blackboard whenever it is feasible.

Finally, another important question in conducting physiological lecture courses is, whether and to what extent shall theories and hypotheses find application? There are many who consider it a transgression if "improved hypotheses" are spread abroad in teaching. In defense it may be said that there is no such thing as physiological instruction without theories and hypotheses. I have shown at the outset that physiology, on account of the many difficulties to be overcome in investigating biological hypotheses in order to unite facts under general points of view, to bring about some connection between them, must, by experiments that originate in hypothetical reflections, arrive at new facts. For the same reason that physiological investigation makes use of working hypotheses, physiological instruction demands consideration of such hypotheses, if this is not to come down to a worthless enumeration of disconnected, barren, isolated facts from which no visualized lasting pictures of the processes in the body can be gained.

Frequently it is only through consideration of theoretical and hypothetical conceptions in physiology that it becomes intelligible how attention was directed to some important problem in physiological investigation and why certain experiments were instituted, all of which would otherwise seem unprovoked and inconsistent. Theory and working hypotheses form the mental bond that combines the several facts to complexes of coherent consistency. But physiological instruction is under obligation to sift clearly between fact and hypothesis. The student is therefore not to be surprised at such ex-

pressions as "this is yet unknown," "this question is still in total obscurity," "the following idea, with some degree of probability has been temporarily advanced," etc.

The physiological laboratory work is an indispensable complement to the lecture course, and that for various reasons. The best theoretical instruction, the most lucid and most perspicuously comprehensive demonstration will not accomplish what an individual preparation, what an experimental contrivance, personally instituted from start to finish, what an operation individually performed can do for the agent. Not by being shown how, but by completely doing, do we learn actual mastery. In consideration of the time, only a limited range of experiments and demonstrations can be produced in the lecture, and that only after careful and conscientious preparation. The student does not see the preparation, he never learns of the many details requisite, he is not aware of the great amount of circumspect forethought that the simplest physiological experiment entails. The instructor, who is constantly manipulating on the other hand, often takes no account of the many little requirements that he meets mechanically, and easily neglects to call attention to more important points. There is no answer to the questions that may arise during the lecture. For all this the physiological laboratory offers a compensation. Here the student conducts all those experiments witnessed in the lecture room and some that could not be produced in the short time of forty-five minutes.

Of course, some physiological knowledge is necessary for all this, hence the laboratory ought not to be open to the student until the second year of physiological instruction. But there is another reason for laying great stress on practical exercises, and that is, their technical side. According to experience many of the younger physicians have had but little opportunity up to the final examination to acquire a certain amount of dexter-



ity, care, and cleanliness in the handling of apparatus, instruments, chemical reagents, living objects, etc. But these are all things that engage the physician constantly in his practice. Without their unfaltering and absolute mastery he would have, not only to renounce many methods of investigation and treatment, but he would commit one of the worst blunders for a physician striving after a practice, he would forfeit the confidence of his patients by his awkwardness and indecision. Decision, adroitness, dexterity, and cleanliness in bearing, as well as in his manipulations, are the most important external qualifications of a physician.

Working in the anatomical laboratory, which offers a good opportunity for practice in such things, is, however, only onesided. There is, moreover, a difference between performing an operation on a living organism, and doing the same on a bloodless corpse. The young physician will have ample opportunity to experience this. Things look quite different when the blood is coursing through the minutest parts, and in the end the physician will have dealings mainly with living human beings. The physiological laboratory offers a many sided possibility for the exercise of manual dexterity in every possible way. It is for this reason that so many detailed operations on animals are described in my *Manual of Practical Physiology*, which Professor H. J. Hamburger and Doctor Laqueur speak of in such favorable terms in their review of this work (*Biochemisches Zentralblatt*, 1912).

Here there will not only be vivisection, but electrical contrivances, preparations for the microscope, graphic representations of breathing, of blood pressure, of muscle movements, chemical reactions on animal fluids, weighing, measuring, and much more. It is of great value to the student to carry out every detail himself to a nicety, as the simplest manipulation can be of great service.

But beside this practice in dexterity and adroitness in the handling of both live and dead objects,

the physiological laboratory ought especially to offer opportunity for manipulating all things that find constant application in practice. The student is to make albumin, urea, sugar tests, etc., to investigate the properties of normal urine, to examine the fluids of the body under the microscope, to execute subcutaneous and intravenous injections, to tie arteries, to stimulate with electricity, ascertain the intensity and volume of electric currents, etc.

For all these reasons it would seem that the practical laboratory work in physiology is quite indispensable and its pursuance in the second year before the final examinations is highly recommended. In order to make the laboratory work possible, with its great burden on the short time devoted to the study of medicine, its time allowance has been fixed at two periods of three hours each weekly.

If lecture courses and laboratory work are to be considered absolute essentials in the physiological training of a physician, then it must be made possible for those who are not satisfied simply with the required course, and for those who for various reasons could not follow some part or other of the physiological lectures, to be set straight on certain chapters. The physiological "seminary" or the conference and special lectures and courses on minor or major departments of physiology serve this purpose. But opportunity must also be offered to satisfy and promote the somewhat farther reaching interest in physiological questions of some students. This need is met in the individual work performed in the physiological laboratory where instructors and assistants are ready to give the necessary stimulus and aid. Naturally only such will engage in this independent work as have finished with the required instruction and training in physiology. Beside this, the "seminary" should be open even to the younger students who are still attending the regular courses on physiology and who desire some little incentive by being heard on physiological questions.

This "seminary" is not to be a reviewing hour in which to prepare for examination, and for which certain tasks are scheduled and gone through with; it is rather to be an informal chat on some physiological problem of more general interest, on modern points of view, on physiological questions of the day, on important news in physiological literature, on various interpretations, opinions, issues in physiological problems, on the more interesting and more important parts of the general lectures and courses, in short, on anything that may claim attention physiologically. The sole object is to arouse interest in physiological problems and to introduce men to physiological ways of thinking.

In this unconstrained form, lacking all didactic varnish, a number of physiological visualizations, teachings, and facts will unconsciously be absorbed and assimilated, with which the formal lectures would probably not have familiarized, and all this without the impression of having been at work. An incentive is perhaps the best that research work and teaching in the science can offer. Truths are only relative and change with time. But interest begets development and development is progress.

If I were asked to express the secret of effective physiological laboratory work in one word I should say—*punctiliousness*.







Sonder-Abdruck aus

# Zeitschrift für biologische Technik und Methodik

Unter Mitwirkung von Fachgenossen

herausgegeben von

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Professor an der Universität in Straßburg i. E.

**Dr. med. et phil. John C. Hemmeter**, Professor der Physiologie an der Universität von Maryland, Baltimore (Aus dem Biol. Marine-Laboratorium d. U.S. Bureau of Fisheries zu Woods Hole, Mass.): Operative Technik der gekreuzten (reziproken) Zirkulation zwischen den Herzen zweier Selachier (*Scyllium*, *Mustelus canis* oder *Carcharias littoralis*). Beziehungen dieser Methodik zur Chemie des Vagus-Problems. Mit einer Figur . . . . .



LEIPZIG  
VERLAG VON JOHANN AMBROSIOUS BARTH  
1913.

Die „Zeitschrift für biologische Technik und Methodik“ erscheint in zwanglosen Hefen (6—8), die zu Bänden von etwa 25 Druckbogen vereinigt werden. Der Preis des Bandes beträgt M 15.—. Der Inhalt zerfällt in:

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- III. Sammelreferate.

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Die Originalmitteilungen sollen, dem Charakter der Zeitschrift gemäß, das Technische und Methodische biologischer Untersuchungen, Apparate und Verfahren, Kurs- und Vorlesungsversuche u. dgl. enthalten. Ihr Umfang soll im allgemeinen  $\frac{1}{2}$  Druckbogen nicht überschreiten.

In die Abteilung „Notizen aus der Arbeits- und Lehrpraxis“ werden kurze Mitteilungen aus Laboratorien und Instituten über dort erprobte Verfahren und Einrichtungen aufgenommen. Es liegt in der Natur der Sache, daß manches davon keinen Anspruch auf völlige Neuheit wird machen können.

Die Sammelreferate berichten in größeren zeitlichen Abständen über die technischen Fortschritte auf einzelnen Gebieten.

Das Honorar beträgt pro Druckbogen M 30.—. Von jeder Arbeit werden dem Verfasser 50 Sonderabzüge kostenfrei geliefert.

Es wird gebeten, die Abbildungen in solcher Ausführung einzuliefern, daß sie photographisch reproduziert werden können (Zeichnungen werden in der Reproduktion gewöhnlich besser als Photographien. Sie sind mit schwarzer Tusche auf weißem Papier herzustellen). Alle Abbildungen werden, wenn irgend möglich, im Text gebracht, nicht auf besonderen Tafeln.

Die Zeitschrift umfaßt alle biologischen Spezialwissenschaften, soweit sie sich des Experiments bedienen (**Physiologie der Tiere und der Pflanzen, physiologische Chemie, Bakteriologie, Serologie, Pharmakologie, experimentelle Pathologie, experimentelle Psychologie, experimentelle Morphologie, Entwicklungs- und Vererbungslehre**).

Die **mikroskopische Technik** (Einbetten, Färben, Schneiden) und die **medizinisch-therapeutische Technik** wird nicht berücksichtigt.

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Der erste Band dieser Zeitschrift, der 1908/09 erschien (454 Seiten mit 161 Abbildungen im Text und einer Tafel, sowie Ergänzungsheft, 34 Seiten mit einem Plane und 20 Abbildungen, zusammen M. 17.80) enthält folgende Originalmitteilungen:

**J. Rich. Ewald** (Straßburg): Über Verwendung rotierender Spiegel zu physiologischen Untersuchungen. I. Das Zykloskop. Mit 3 Figuren.

**Dr. Wilhelm Berndt** (Berlin): Apparat zum Aufhängen und Aufbewahren von Wandtafeln. Mit 5 Figuren.

**Prof. T. Thunberg** (Lund): Über die Anwendung eines Platinbrenners zum Schreiben auf Glas und für ähnliche Zwecke. Mit 1 Figur.

**Prof. Wilhelm Roux** (Halle a. S.): Eine Methode der Selbstkopulation von Tropfen. Mit 1 Figur.

*Fortsetzung auf der 3. Umschlagseite.*

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*Sonder-Abdruck aus*  
**„Zeitschrift für biologische Technik und Methodik“.**  
*1912. Band II. Nr. 8.*  
*Verlag von Johann Ambrosius Barth in Leipzig.*

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(A. d. Biol. Marine-Laboratorium d. U. S. Bureau of Fisheries zu Woods Hole, Mass.)

# **Operative Technik der gekreuzten (reziproken) Zirkulation zwischen den Herzen zweier Selachier (*Scyllium*, *Mustelus canis* oder *Carcharias littoralis*). Beziehungen dieser Methodik zur Chemie des Vagus-Problems.**

Von

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(Mit einer Figur).

In den letzten zwanzig Jahren gewinnt die Lehre von der Chemie der Vagusinhibition des Herzens immer mehr an Wichtigkeit. Man behauptet geradezu, daß Herzverlangsamung und Herzstillstand nach Vagusreizung von Chlorkalium (KCl) abhinge, welches unter dem Einfluß der Vagusreizung in dem Myokardium frei würde. Durch eine solche Auffassung wird natürlich der direkte Einfluß des Vagus auf den Herzmuskel ausgeschlossen. Die Lehre der Vagus-Kalium-Inhibition hat manches Bestechende an sich<sup>1)</sup>.

Ist nun die Herzverlangsamung und der Stillstand in letzter Instanz durch eine im Plasma gelöste Substanz verursacht, so muß das Blut eines inhibierten Herzens auch ein anderes (zweites) Herz verlangsamen können, wenn es in dieses hineingeleitet wird. Es ist zu diesem Zweck wünschenswert, daß das Blut, welches zur Zeit der Vagusreizung und des Herzstillstandes durch Vorhof und Kammern eines Tieres strömt, von diesem abgeleitet und durch das Herz eines zweiten Tieres derselben Art geführt wird. Durch diesen Gedanken gewinnt die physiologische Technik einer gekreuzten (reziproken) Zirkulation zwischen den Herzen zweier Tiere an Wichtigkeit. Ich verwandte dazu die an der Marinestation (U. S. Bureau of Fisheries) zu Woods Hole, Mass., vorkommenden Selachier *Mustelus canis* (Dogfish) und *Carcharias littoralis* (Sand-

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<sup>1)</sup> Siehe Nagels Handbuch der Physiologie, ferner v. Cyon: Die Nerven des Herzens, und Howell, Textbook of Physiology, und des letzteren Veröffentlichungen im Americ. Journ. of Physiol.

shark) aus Gründen, die ich schon früher in dieser Zeitschrift<sup>1)</sup> angegeben habe. Ich verweise auf diesen Artikel in bezug auf die Herz- und Vagusisolierung bei diesen Fischen und auf die Narkose usw.

**Beschreibung der Operation.** Zwei sehr gesunde Sandhaie (*Carcharias littoralis*), die aus den Fallen in die Station gebracht waren, werden um 9.39 Vorm. in ein großes Aquarium mit Seewasser gesetzt. Nachdem sie lebhaft herumgeschwommen sind, benehmen sie sich auch bei der Äthernarkose sehr lebhaft und setzen dieser beträchtlichen Widerstand entgegen.

Die Herzen werden nach der vom Autor beschriebenen Technik freigelegt. Ein Ramus cardiacus vagi (in manchen Versuchen auch beide) wird nach der in dem besagten Artikel (S. 221) beschriebenen Weise freipräpariert und auf Fäden genommen. Dann werden Kanülen in das proximale und das distale Ende des Haies Nr. 1 der thorakalen Aorta eingebunden, ebenso in die laterale Abdominalvene des Haies Nr. 2 und in das proximale Ende der Aorta thoracalis desselben Tieres<sup>2)</sup>.

Das proximale Ende der abdominalen oder besser thorakalen Aorta von Hai Nr. 1 wurde mittels einer Kanüle mit der rechten lateralen Abdominalvene von Hai Nr. 2 verbunden. Die Kanüle wurde in der Vene so weit als irgend möglich vorgeschoben; sie war dann im Cuvierschen Sinus zu fühlen. Durch Klemmpinzetten wurde die Zirkulation verhindert, bis alle Verbindungen der gegenseitigen Transfusion hergestellt waren. Durch die eben beschriebene Verbindung konnte das Blut von Tier Nr. 1 in das Herz von Nr. 2

<sup>1)</sup> Zur Technik von Vagusexperimenten am Herzen von *Scyllium* usw. Diese Zeitschrift Bd. 2, S. 221, 1911.

<sup>2)</sup> Als gerinnungshemmendes Mittel wurde Hirudin verwandt. Es ist das eine kostspielige Substanz; ein Gramm kostet 12 Dollar, ein Dezigramm 2,75 Dollar. Letztere Menge reicht hin, um das Blut von drei Haien von je zwei Kilo Gewicht gerinnungsunfähig zu machen. Bei einem Hai beträgt die Blutmenge  $\frac{1}{10}$  des Körpergewichts; ein Tier von 2000 g enthält also 200 g Blut. Um dieses gerinnungsunfähig zu machen, braucht man 0,04 g Hirudin. Es wurde eine Lösung von 0,1 Hirudin in 25 ccm Salzlösung hergestellt und davon 10 ccm verwendet. Bei einem Versuch begnügten wir uns mit einer Lösung von 0,01 g Hirudin in 100 ccm Ringerscher Lösung; mit dieser Flüssigkeit durchspülten wir die Kanülen, Gummischläuche und Glasröhren vor dem Versuch. Innerhalb von zwei Stunden bildete sich dann kein Gerinnsel. Es dürfte unnötig sein, das gesamte Blut des Tieres gerinnungsunfähig zu machen, weil das zu viel Hirudin erfordert. Es genügt ja, wenn es nicht innerhalb der Schläuche und Röhren gerinnt. Hirudin beeinflusst durchaus nicht die Vagushemmung, da diese vor und nach der Injektion des Mittels dieselbe bleibt.

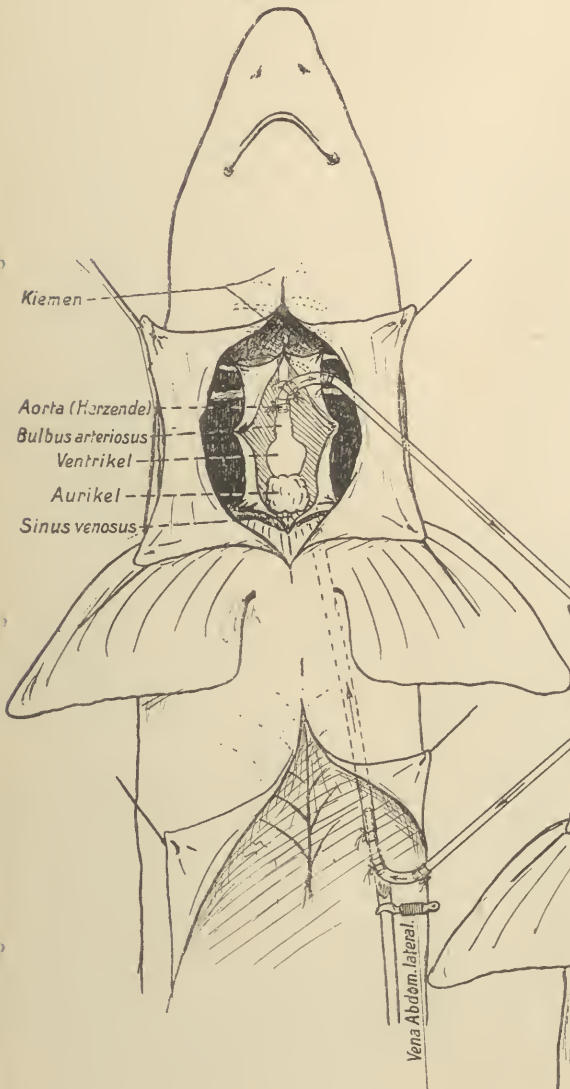
geleitet werden; aber es mußte nun noch dafür gesorgt werden, daß es wieder von Nr. 2 zu Nr. 1 zurückkam und in den Kiemen des letzteren Tieres mit Sauerstoff versorgt wurde. Zu diesem Zwecke wurde eine Verbindung zwischen dem proximalen Ende der Aorta thoracica von Nr. 2 und dem distalen Ende desselben Gefäßes von Nr. 1 angelegt. Nun macht das Blut folgenden Weg: Aus dem Ventrikel von Nr. 2 durch die Aorta und die Schlauchverbindung zu dem distalen Ende der Aorta von Nr. 1, von da zu den Kiemen und zurück zu dem Herzen desselben Tieres (durch seine eigene Dorsalaorta).

Die gekreuzte Zirkulation verläuft im ganzen nun folgendermaßen: Von dem Herzen von Nr. 1 in die ventrale Aorta, durch die in dem proximalen Ende derselben steckende Kanüle und die Schlauchverbindungen zu der lateralen Abdominalvene, dem Cuvierschen Sinus, dem Sinus venosus und dem Herzen von Nr. 2. Aus diesem in die Abdominalaorta desselben Tieres, aus dieser in die darin eingebundene Kanüle, durch den Schlauch zurück zu Nr. 1, aber jetzt zu dem distalen Ende der abdominalen Aorta. Von hier gelangt es in die Kiemen dieses Tieres (Nr. 1), die unter Seewasser gehalten wurden, durchheilt die Dorsalaorta und den allgemeinen Körperkreislauf (hinab zum Schwanz und den Eingeweiden) und kommt dann schließlich in den Sinus venosus und das Herz (von Nr. 1) zurück. Ein Teil des Blutes geht jedoch von den Kiemen direkt in das Herz zurück. Hier in diesem Herzen wird das Blut beider Tiere bis zu einem gewissen Grade gemischt. Mit Hilfe einer Stopuhr wurde immer genau bestimmt, wie lange Zeit das Blut des Haies Nr. 1 brauchte, um den Weg von der Kanüle im proximalen Ende der Aorta von Nr. 1 zum Sinus venosus von Nr. 2 zu durchlaufen. Zu diesem Zwecke wurden alle Verbindungen soweit es irgend anging aus Glas hergestellt und Gummi nur dort verwendet, wo es nicht anders möglich war. Wenn jetzt die besagte Kanüle und die daran befestigte Rohrverbindung mit Haiserserum angefüllt war, konnte das Vorrücken des Blutes deutlich beobachtet werden. Die Zeit, in welcher der fragliche Weg zurückgelegt wird, hängt ab 1. von Kraft und Frequenz der Herztätigkeit, 2. von der Weite und 3. von der Länge der Rohrverbindung. Beim Beginne unserer Versuche nahmen wir zu weite und zu lange Röhren, und uns fehlte die nötige Übung im Einbinden der Kanülen, in der Vermeidung von Luftblasen und in der Herstellung dichter Verbindungen. Deshalb mißlangen uns mehrere Versuche.

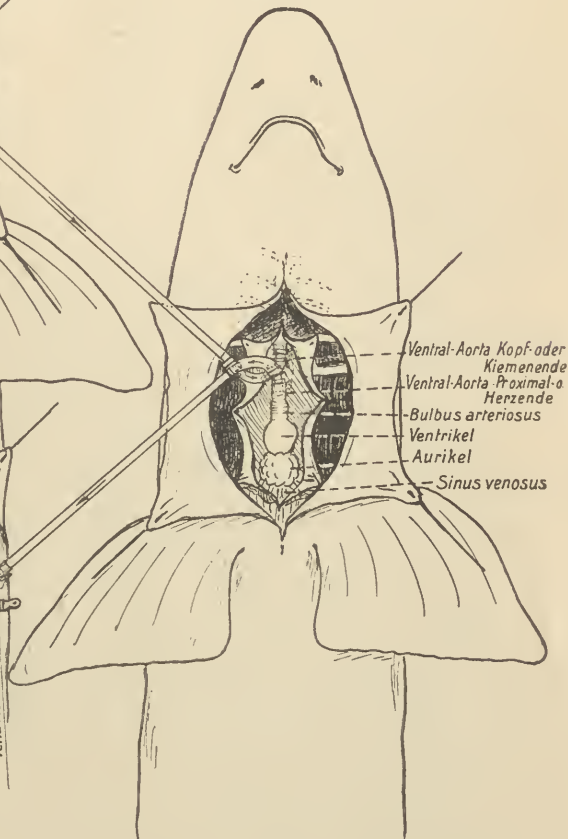
Die nach obiger Methode bestimmte Zeit mußte zu dem Mo-

mente, wo die Reizung des Vagus von Tier Nr. 1 aufhörte, hinzugerechnet werden, wenn man an den registrierten Kontraktionen

Nº 2.



Nº 1.



des Herzens Nr. 2 beurteilen wollte, ob dieses durch irgend eine vom Herzen Nr. 1 herüberfließende chemische Substanz gehemmt



würde. Denn das Blut, welches das verlangsamte oder gehemmte Herz Nr. 1 passiert hat, muß ja erst die Kanülen, die Schläuche und die laterale Abdominalvene von Nr. 2 durchströmen, ehe es das Herz des zweiten Tieres erreicht. Während vollständiger Hemmung des ersten Herzens strömt natürlich kein Blut über.

Beide Herzen wurden zu gleicher Höhe gehoben, und die Kontraktionskurven eines jeden wurden auf dem Kymographium registriert, indem die äußerste Spitze des Ventrikels durch einen Faden mit dem Schreibhebel verbunden wurde. Der Vagus des Tieres Nr. 1 wurde isoliert und durch einen Faden (nicht zu dünn, damit er nicht durchschnitten) gehalten. Gereizt wurde mit einem Harvard-(du Boisschen) Induktionsapparat und einem Strom von 7 Volt. Rollenabstand 10 cm. Vagusreizung verursachte prompten Herzstillstand. Einmal wurde das Herz 1 Min. 6 Sek. gehemmt, so daß es in dieser Zeit nur zwei Schläge ausführte. Aber niemals zeigte die Kurve von Nr. 2 irgend eine Veränderung in bezug auf Rhythmus, Geschwindigkeit oder Kraft. Als nach dem Verlauf von 1 Stunde 16 Minuten die Kanülen entfernt wurden, floß aus ihnen allen das Blut ganz frei aus. In dieser Art wurden fünf gelungene Versuche angestellt, die sehr befriedigende Kurven ergaben. Die Zeit wurde mittels eines elektrisch registrierenden Metronoms unter den Herzkurven aufgeschrieben.

Während des völligen Herzstillstandes kann kein Blut aus dem gehemmten Herzen nach dem andern gelangen, weil das erstere sich nicht kontrahiert und das Blut deshalb stillsteht; aber sobald die Vagusreizung aufhört und das Herz seine erste Kontraktion macht, beginnt auch die Zirkulation wieder. Deshalb ist es nötig, auf den Kurven genau die Zeit zu markieren und besonders den Zeitpunkt zu bezeichnen, wo der Ventrikel den ersten Schlag ausführt. Beim Selachierherz gehen die Koronararterien nicht direkt vom Ventrikel ab; wenn das so wäre, könnte der Herzmuskel nicht gehörig mit sauerstoffhaltigem Blut versorgt werden, denn das Ventrikelblut ist weitgehend gemischt, in Wirklichkeit mehr venös als arteriell, und wird zur Versorgung mit Sauerstoff erst durch die Kiemen getrieben. Die Koronararterien kommen erst von den Kiemen zurück; man kann sie sehen, wie sie der Oberfläche der ventralen Aorta anliegen<sup>1)</sup>.

Die Koronararterien bei diesen Elasmobranchiern sind also zum größten Teil Gefäße, welche von außen an das Herzgewebe heran-

<sup>1)</sup> Siehe G. H. Parker, The blood vessels of the heart in *Carcharias*, *Raja* and *Amia* Proceed. of the Boston Soc. of Nat. History, 1899, Bd. 29, Nr. 8.

kommen und von Ästen der medianen Hypobranchialarterie abgegeben werden. Wenn der Ventrikel sich kontrahiert, so geht das ausgepreßte Blut zuerst durch den Bulbus arteriosus, dann durch die ventrale Aorta, dann durch das komplizierte System der Branchialgefäße, dann zurück durch die Verbindung von Kommissuralarterien, von welchen die wichtigsten die A. mediana hypobranchialis heißt, um schließlich die afferenten Koronararterien zu bilden<sup>1)</sup>.

Ich betone das, um darzutun, daß es mindestens 3—6 Sekunden dauern muß, ehe das bei einer gegebenen Systole ausgetriebene Blut als Koronarblut zum Ventrikelmuskel zurückkommen kann, um diesen mit Sauerstoff und den sonstigen zur Kontraktion nötigen Stoffen zu versehen. Es ist wohlbekannt, und man kann es auch an den mit der beschriebenen Methode aufgenommenen Kurven sehen, daß das Herz schon eine Sekunde nach der Vagusreizung vollständig gehemmt sein kann. Sicher vergeht in einigen Kurven nicht mehr als eine Sekunde zwischen der Reizung und dem vollständigen Stillstand. In Wirklichkeit mag die Zeit noch kürzer sein, da es nicht möglich ist, mit absoluter Genauigkeit die Latenzzeit der Vagusreizung aufzuzeichnen. Sie hängt ab von der Frequenz des Herzschlages; z.B. bei einer Frequenz von 30 pro Minute können zwei Sekunden vergehen, ehe der Effekt der Reizung sichtbar ist.

Da einige Sekunden dazu nötig sind, bis das Blut die Bronchialzirkulation erreicht und zurück zum Herzen kommt, ist nicht einzusehen, wie die Herzhemmung durch einen im Herzen entstehenden chemischen Stoff verursacht sein sollte. Man müßte schon annehmen, daß er zuerst in die Gefäße von Thebesius eintritt, welche freier mit den Koronarvenen als den Koronararterien kommunizieren. Wenn die Hemmung aber von einem chemischen Stoff herrührt, so muß er das Myokardium durch die Kapillaren verlassen, dann in die Venen gelangen, dann bei der nächsten Systole aus dem Herzen ausgetrieben werden, dann durch die Kiemen gehen, um schließlich durch die Koronararterien das Herz wieder zu erreichen. Doch zu all diesem ist eine längere Zeit nötig, als die Herzhemmung erfordert. Mit anderen Worten: der Herzmuskel dieser Selachier wird nicht von Blut durchströmt, welches bei jeder Systole aus dem Ventrikel selbst kommt, sondern die Systole sendet das Blut erst zu den Kiemen, und es muß erst von da durch die Koronararterien wieder zurückkommen, um das Herzfleisch zu ver-

<sup>1)</sup> Parker l. c. p. 164.

sorgen. Wenn diese Bronchialzirkulation eine längere Zeit erfordert als der Eintritt der Herzhemmung durch den Vagus, dann kann der Herzstillstand nicht einem unter dem Einfluß der Vagusreizung im Myokardium produzierten Stoff zugeschrieben werden. Dieser Punkt verdient Beachtung, da man ja die Lehre aufgestellt hat, daß die Vagushemmung von der Produktion von KCl im Myokardium herrühre.

Die oben beschriebene Technik läßt sich selbstverständlich auch durchführen, wenn man anstatt des normalen Blutes Salzlösung mit Harnstoff durchzirkulieren läßt. Nach Baglioni<sup>1)</sup> ist der Harnstoff eine unentbehrliche Substanz, um die Herzaktion der Selachier zu erhalten. Aber jedenfalls ist es einwandfreier, wenn man mit dem natürlichen Blut arbeitet.

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<sup>1)</sup> Zeitschrift für allg. Physiologie, Bd. 6, S. 70: Einfluß der chemischen Lebensbedingungen auf die Tätigkeit des Selachierherzens.

- H. Zwaardemaker (Utrecht): Die Herstellung von Mischgerüchen. Mit 2 Figuren.  
 O. Langendorff (Rostock): Ein Versuch zur allgemeinen Muskelphysiologie. Mit 2 Figuren.  
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 T. Graham Brown (Straßburg): Eine neue Methode, Herzbewegungen bei Tauben zu registrieren. Mit 1 Figur.  
 Raymond Pearl Ph. D. und F. M. Surface Ph. D. (Orono, Maine, U.S.A.): Apparate und Methoden, die bei experimentellen Untersuchungen über Vererbung beim Geflügel gebraucht werden. Mit 11 Figuren, davon 8 auf einer Tafel.  
 Gustav Bayer (Innsbruck): Zur Technik der Produktion von Kreislaufstörungen. Mit 1 Figur.  
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 A. Pi Suñer (Barcelona): Über eine physiologische Lokalisationsmethode in den nervösen Zentren.  
 Die Biologische Versuchsanstalt in Wien. Zweck, Einrichtung und Tätigkeit während der ersten fünf Jahre ihres Bestandes (1902—1907), Bericht der zoologischen, botanischen und physikalisch-chemischen Abteilung, zusammengestellt von Hans Przibram. Mit 28 Figuren und 1 Plan.

Der zweite Band (384 Seiten mit 128 Abbildungen im Text und 1 Tafel, 1910—12) enthält folgende Originalarbeiten:

- Prof. Dr. W. Lindemann (Kiew): Über die Methodik der intrathorakalen Operationen an Tieren. Mit 1 Figur.  
 Reinhard von den Velden (Düsseldorf): Einfache Laboratoriumsapparatur zur Vornahme von Überdruckoperationen. Mit 1 Figur.  
 J. K. Njegotin (Jurjew-Dorpat): Unblutiges Verfahren, das Froshherz freizulegen. Mit 3 Figuren.  
 Prof. Dr. J. P. Karplus und Prof. Dr. Alois Kreidl (Wien): Eine Methode zur Freilegung der Hirnbasis. Mit 2 Figuren.  
 Dr. M. Ponzo (Turin): Über eine einfache Vorrichtung, um Photographien und Zeichnungen plastisch zu sehen. Mit 1 Figur.  
 H. G. Cannegieter (Utrecht): Leitendmachen dünner Quarzfäden durch Kathodenzerstäubung mit nachfolgender galvanischer Versilberung. Mit 2 Figuren.  
 Dr. med. Eugen Weber (Kiew): Über die Möglichkeit gleichzeitiger quantitativer Bestimmungen zweier Gallenfarbstoffe in der Galle mit Hilfe des Spektrophotometers.  
 Karl L. Schaefer: Ein Apparat für Demonstrationen und Versuche über den blinden Fleck. Mit 1 Figur.  
 Martin Gildemeister (Straßburg i. E.): Über Zählen und Zeitschätzen.  
 J. Rich. Ewald (Straßburg): Die Anfertigung des Nerv-Muskelpräparates und des Schenkelpräparates des Froshes. Mit 4 Textfiguren.

Fortsetzung auf der 4. Umschlagseite.



- Hans Kulep: Eine neue Vorrichtung für intermittierende Reizung am Klinostaten. Mit 3 Abbildungen.
- Privatdozent Dr. J. Strohl: Wesen und Wert des Dezimalsystems in der Bibliographie.
- R. Magnus: Zur Verpflegung der rückenmarksoperierten Tiere.
- Spektroskopie im Praktikum. Mit 1 Figur.
- Prof. Dr. G. van Rynerk (Amsterdam): Ein Demonstrationsverfahren zur Erläuterung des Schließungsmechanismus der Semilunarklappen des Herzens. Mit 2 Figuren.
- Prof. Dr. Sommer (Gießen): Zur Verbesserung der elektromedizinischen Methodik. Mit 1 Figur.
- H. Kronecker (Bern): Der Kapillarsphygmograph. Mit 4 Figuren.
- Dr. Alberto Mochi (Siena): Die plethysmographische Registrierung der Atmung des Frosches. Mit 3 Figuren.
- Ernst G. Pringsheim: Die Kultur von Wurzeln auf Löschpapier als physiologisches Hilfsmittel. Mit 5 Figuren.
- Ernst Willy Schmidt: Methoden der Untersuchung anaerober Bakterien. Mit 4 Figuren.
- C. C. Guthrie (Pittsburg): Über Ausschaltung der höheren Zentren zu physiologischen Zwecken. Mit 5 Figuren.
- Dr. A. Gröber (Berlin): Ein neuer Tropfenzähler. Mit 2 Figuren.
- Ernst Willy Schmidt (Marburg): Nachtrag zu der Arbeit „Methoden der Untersuchung anaerober Bakterien“. Mit 4 Figuren.
- A. Durlg (Wien): Zur biochemischen Methodik. Mit 4 Figuren.
- Privatdozent Dr. Walter Hausmana (Wien): Toxikologische Vorlesungsversuche.
- Dr. F. Ichak und H. Friedenthal (Nikolassee): Über graphische Darstellung von Wachstumserscheinungen. Mit 4 Figuren.
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- Dr. Leone Lattes (Turin): Eine Methode zur Herstellung kontinenter Pankreas-Dauerfisteln.
- Dr. med. et phil. John C. Hemmeter (Baltimore): Operative Technik der gekreuzten (reziproken) Zirkulation zwischen den Herzen zweier Selachier (Scyllium, Mustelus canis oder Carcharias littoralis). Beziehungen dieser Methodik zur Chemie des Vagus-Problems. Mit 1 Figur.

# Priority of Employment of the Roentgen Ray in Studying the Physiology and Path- ology of the Digestive Tract

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JOHN C. HEMMETER, M.D., PHIL.D., LL.D.  
BALTIMORE

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*Reprinted from The Journal of the American Medical Association  
October 5, 1912, Vol. LIX, pp. 1308 and 1309*

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CHICAGO



**Priority of Employment of the Roentgen Ray  
in Studying the Physiology and Path-  
ology of the Digestive Tract**

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JOHN C. HEMMETER, M.D., PHIL.D., LL.D.  
BALTIMORE





Priority-of Employment of the Roentgen Ray in Studying the  
Physiology and Pathology of the Digestive Tract

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*To the Editor:*—In June, 1896, an article appeared in the *Boston Medical and Surgical Journal*, page 609, entitled "Photography of the Human Stomach by the Roentgen Method," by John C. Hemmeter. This report, although not published until two months after it was sent to this journal (for I received acknowledgment of its acceptance April 10, 1896), is printed under the date of June 18, 1896.

This antedates any other publication on this subject in the English language. Wolf Becker (*Deutsch. med. Wchnschr.*, March 26, 1896) at about the same time had experimented on the stomachs of animals by filling them with solutions of lead acetate (sugar of lead) after laparotomy, and in doing so he tore the walls of the stomach, which were sewed up again, but not so tightly as to prevent leakage. The solution therefore leaked out into the abdominal cavity and only a diffuse, badly defined photograph was obtained by the *x*-rays. In April of the same year Carl Wegele (*Deutsch. med. Wchnschr.*, July, 1896) had advised experimentation with a spiral metallic electrode introduced into the stomach. His paper was merely a suggestion—he did not report that he had produced any real skiagrams of the stomach; in fact, by this method it was impossible to make them. One might photograph the electrode, but not the stomach. Becker from his own statements worked only on animals and Wegele could produce no photographs whatever of the stomach.

In 1896 I had already made skiagrams of the entire stomach by the method described in the *Boston Medical and Surgical Journal*, June 18, 1896. The work was done in the physical laboratory of the State Normal School in Baltimore with the assistance of the professor of physics at that time, Prof. A. Hammer, and my associate, Dr. Harry Adler. The work was elementary and there were failures that were unavoidable with the apparatus available sixteen years ago. It cannot be denied, however, that *x*-ray photography of the digestive canal was originated as pioneer work then and there, and the work of Rieder, Haudek, Holzknecht and other meritorious clinicians in Germany and this country came after mine. It has occasionally been asserted even by American writers that the *x*-rays were not employed in the diagnosis of precisely stated conditions of the digestive tract until 1907, and then only by Germans. It has been acknowledged by Ewald and Boas as well as Haudek and the entire school of clinical medicine in Vienna, where most of this special kind of clinical radiology is now done, that the first employment

of *x*-rays for the diagnosis of ulcer of the stomach was conceived and undertaken by me.

In fact, I possess letters of appreciation and congratulation from my friends, Professors Ewald and Boas of Berlin, in which they compliment me and my co-workers as being the pioneers of this special type of radiology. The main reason why they are so conversant with the history and character of the radiologic work of my clinic is to be found in the fact that I published the first complete account of it in a German journal (*Neue Methoden zur Diagnose des Magengeschwürs*, *Arch. f. Verdauungskr.*, 1905, xii, No. 5, p. 357; also *Experimente welche die Möglichkeit demonstrieren Läsionen der gastrischen Mucosa durch X-Strahlen sichtbar zu machen*, *ibid.*, p. 360; also *Demonstration des Magengeschwürs beim Menschen mittelst der Bismuth Subnitricum und X-Strahlen Methode*, *ibid.*, p. 362, 1906).

Since then I have added nothing new to the first method, for all later advancement has consisted in the improvement of apparatus—unless one is willing to accept as an advancement the use of calcium carbonate and calcium phosphate or of aluminum silicate instead of bismuth salts as first used by me. Leading German, Austrian and French clinicians have in the friendliest terms conceded to my clinic the historic priority of the methods of special radiology mentioned in the preceding. Furthermore, in the German article of July, 1906, (*Arch. f. Verdauungskr.*, xii, p. 363), I pointed out that the method was useful in the diagnosis of carcinoma of the stomach but that it had failed in two cases of cholelithiasis in which the gall-stones were later removed at operation.

Prof. Harry Adler and Dr. Robert Bay have repeated my experimental and clinical work in gastric radiology and Dr. Adler published his first results, which are confirmatory, in *THE JOURNAL* ("The Diagnosis of Ulcer of the Stomach and Duodenum by the Roentgen Ray," Nov. 12, 1910, p. 1725). Adler in this article also reported a number of cases of duodenal ulcer recognized by radiology and found later at operation.

It has sometimes been erroneously stated that Jolasce preceded me in employing radiology for the diagnosis of gastric ulcer. A scrutiny of Jolasce's publication (*München. med. Wchnschr.*, 1907, No. 29) will clearly prove that it appeared more than a year after my contribution to the *Archiv für Verdauungskrankheiten* (July, 1906). The most recent German text-books on diseases of the stomach (Hans Elsner, "Lehrbuch der Magenkrankheiten," p. 286, and also the new edition of Boas) have stated correctly the chronologic sequence of this radiologic endeavor. Other publications by my associates are by Adler and Ashbury (*Am. Roentgen Ray Soc.*, September, 1910; also Adler and Ashbury, *New York Med. Jour.*, Oct. 7, 1911).

JOHN C. HEMMETER, M.D., PHIL.D., LL.D., Baltimore.







# Hyperthyroidosis of Intestinal Origin

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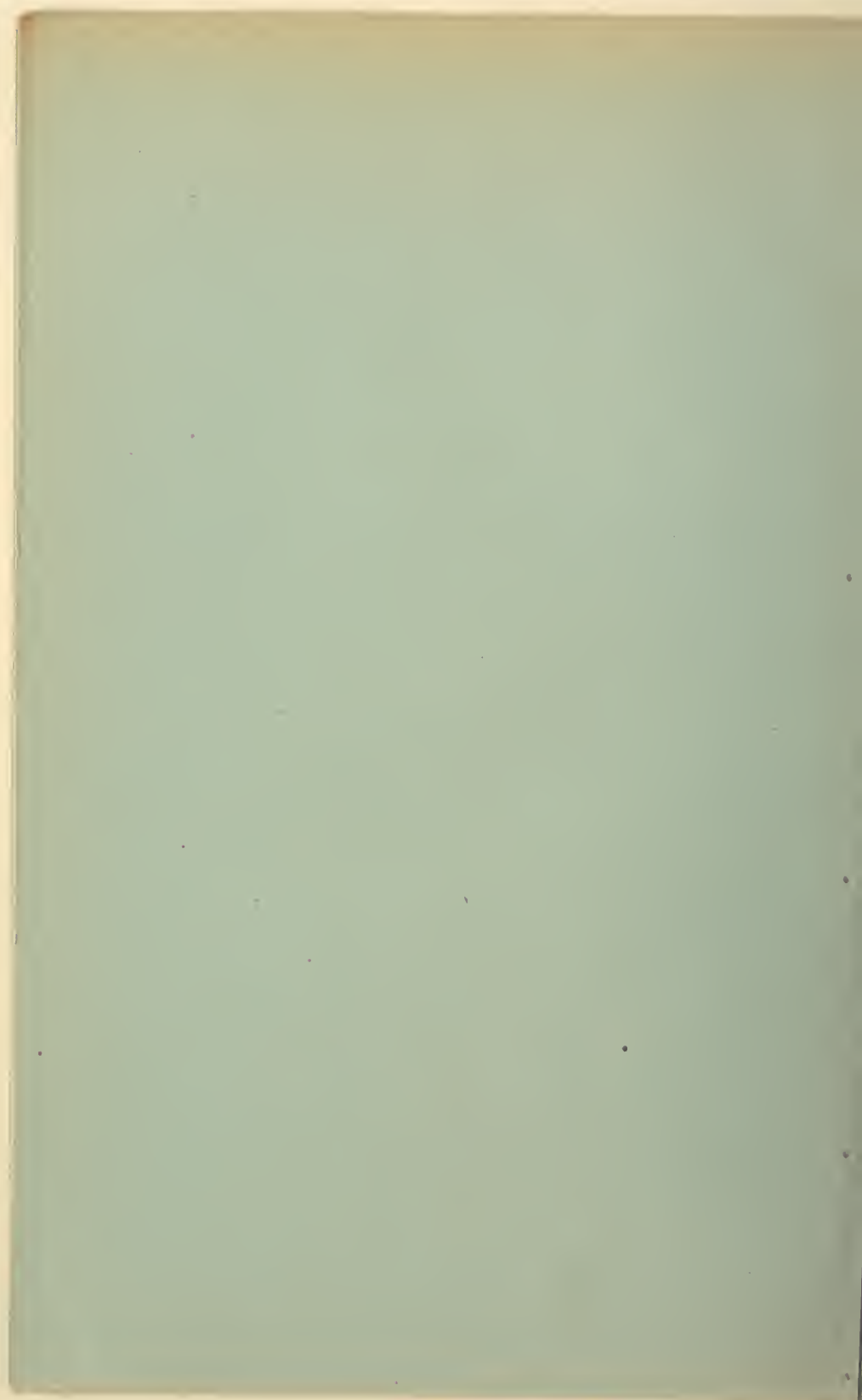
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*Reprinted from The Journal of the American Medical Association  
Dec. 13, 1913, Vol. LXI, pp. 2145 and 2146*

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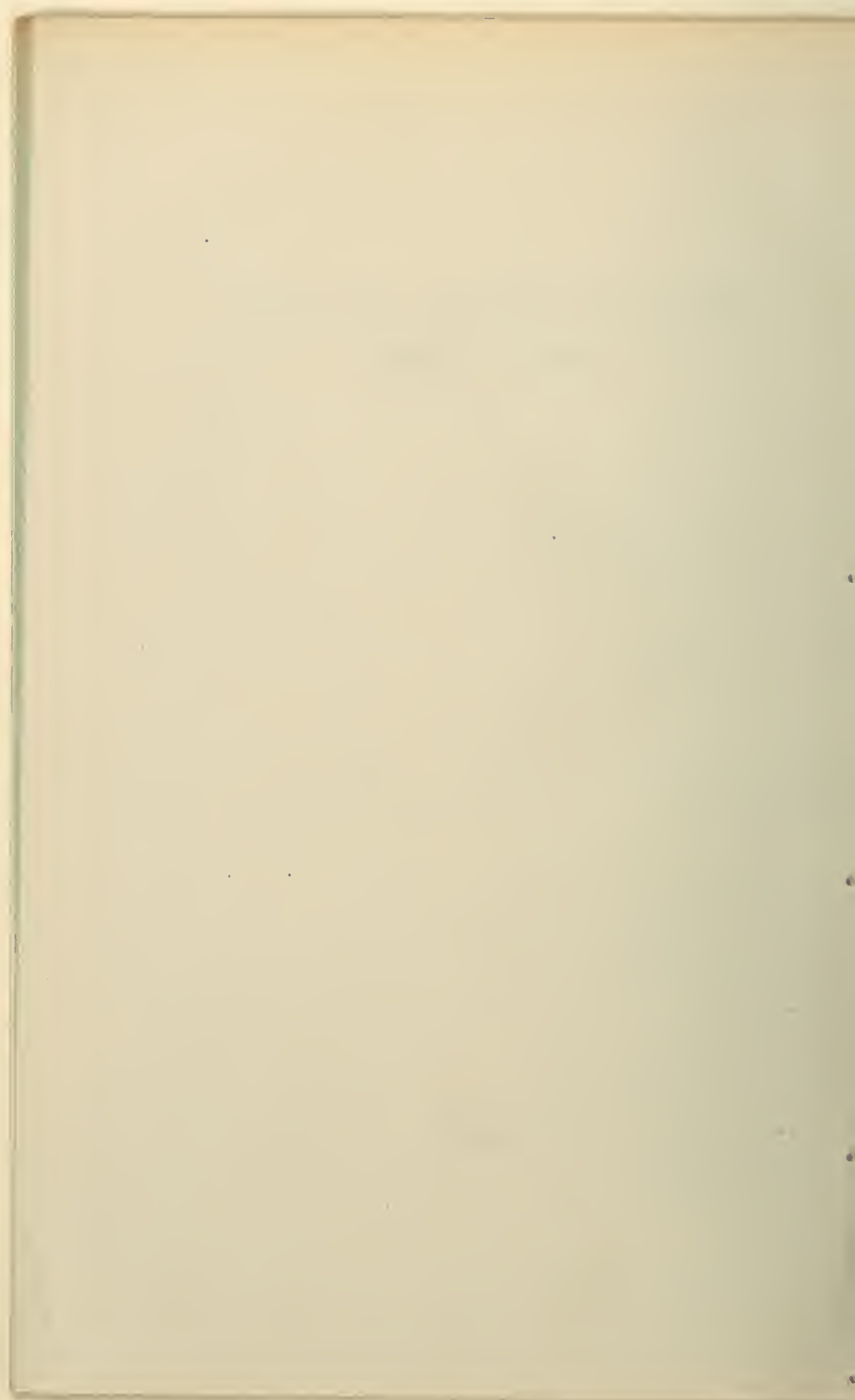


# Hyperthyroidosis of Intestinal Origin

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J. C. H E M M E T E R, M.D., P H. D.  
BALTIMORE





## HYPERTHYROIDOSIS OF INTESTINAL ORIGIN

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J. C. HEMMETER, M.D., PH.D.

BALTIMORE

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The pathogenesis and disarrangement of the internal secretions and defective coordination between these secretions and the nervous system which constitute hyperthyroidism or, when they are in an extreme state, Basedow's disease, are still veiled in obscurity. Whatever the internal disarrangement of a chemical or neurogenic nature may be, it constitutes, for the present, one of the mysterious problems of pharmacology, as well as of physiology and pathology.

When Basedow first published the symptom-complex in 1840, which has since retained his name, he described three classical signs as characteristic of this condition: first, exophthalmos; second, enlargement of the thyroid, and third, tachycardia. At present we could probably safely add two more frequent conditions. These are muscular tremors and disturbances of the gastro-intestinal tract, particularly diarrhea. The diarrhea has since then always been regarded as a consequence of Basedow's disease and I fail to notice in literature that anyone has reported diarrhea, or more precisely, any anatomic change in the gastro-intestinal tract as preceding the classical symptoms of Basedow. Robert James Graves, who worked over the studies of Basedow and confirmed them, nowhere states that a typical Basedow may follow years of gastro-enteric abnormalities. We have as yet no exact physiologic, pharmacologic or pathologic test for the existence of Basedow's disease in its incipency—conditions which are more properly called "thyreoses"; when there is excessive function of the thyroid, the condition is called hyperthyreosis; when diminished, hypothyreosis. I should suggest a third idea where the thyroid secretion is not quantitatively diminished nor increased, but chemically altered into a secretion containing different chemical substances from the normal. I designate this as

*dysthyreosis*. No one denies the facility of the diagnosis when the classical symptoms are pronounced, but usually when such a state of the various organs exists, there are already extensive pathologic changes in most of the internal organs.

In the present state of our knowledge we have principally two views which, though indefinite, might be stated as attempts to explain the internal disarrangement of the secretion of ductless glands and the disturbed reciprocal coordination of nerve-cells with these internal secretions. One is the view held by Moebius that the thyroid is at the bottom of the entire trouble. The other is not definitely associated with any clinician's name, but it is a view which maintains that the thyroid is only secondarily involved and that some other nervous or chemic deviation from the normal has preceded the thyroid abnormality. That pronounced cases of hyperthyreosis, even with exophthalmos and slight enlargement of the thyroid and tachycardia, have been observed where surgical removal of parts of the thyroid could reveal nothing abnormal in the gland itself, is suggestive of the possibility that the thyroid may be secondarily affected.

In a recent article<sup>1</sup> von Noorden describes remote symptoms of a nervous and muscular derangement consequent on intestinal disturbances and even goes so far as to suggest that his associate (Eppinger) has isolated a bacillus from the intestinal contents of such sufferers which is suspected of being the cause of the whole difficulty.

McCarrison's results are mentioned in *THE JOURNAL*<sup>2</sup> as follows:

Having shown in the course of his researches on the etiology of endemic goiter that the infecting agent of this disease exists in the intestinal tract and that a plentiful amebic infection was present in this situation in the vast majority of all cases of goiter in Gilgit [India], McCarrison has been engaged in endeavoring to cultivate amebas from the feces of sufferers from this disease. During the course of this work he was struck with the constant character of the bacillary growths which appeared in the medium employed. This medium was the one recommended by Musgrave for the cultivation of amebas. The vaccine employed was, therefore, a

1. Von Noorden, Carl: Intoxication Proceeding from the Intestines, Especially Polyneuritis, *THE JOURNAL A. M. A.*, Jan. 11, 1913, p. 101.

2. McCarrison's Researches on Goiter, editorial, *THE JOURNAL A. M. A.*, Aug. 10, 1912, p. 449.

composite one and contained organisms capable of growth on an alkaline and feebly nitrogenous medium. This vaccine was administered in selected cases in doses of from 150,000,000 to 350,000,000; the inoculations were made at intervals of from seven to ten days. The results obtained were most gratifying.

Recently Sasaki produced enlargement of the thyroid by feeding normal rats with feces of other normal rats, and he also produced thyroid enlargement by the subcutaneous injection of rat feces. These experiments are quoted from Julius Bauer.<sup>3</sup>

We may interpret these quotations that intestinal abnormalities, though long recognized as a consequence of hyperthyroidism, may also be a cause, even if we limit ourselves to the conception that a live microbe agent is necessary to bring about this effect.

I wish to report three cases in which a chronic colitis of ten, eighteen and twenty years' standing had preceded the symptoms of hyperthyroidism. Two of these patients had been in Carlsbad for the relief of their colitis and one had been operated on, a partial thyroidectomy having been performed with only very transient relief of the symptoms. Naturally it would be desirable if we could find a method of determining when and how a colitis or enteritis is the cause and when it is the result of hyperthyroidism. Unfortunately, we are still lacking biologic and chemical tests for ascertaining the relation of these two states. I had personally hoped for such a test from the research of Dr. Reid Hunt, working in the Department of Pharmacology of the United States Public Health Department, but Dr. Hunt's acetonitril reaction has not proven of diagnostic help. I quote his own words from a letter to me:

I do not think that the acetonitril reaction has at present any value for purposes of diagnosis; it does not seem to be constantly obtained even in marked cases of hyperthyroidism. I hope, however, it contains the germ of a method which may be developed into one of use.

Perhaps as important a conclusion as any can be deduced from the fact that treatment directed to the intestine is more efficacious than treatment by thyroïdin, antithyroidin, or by Beebe's antithyroid serum, and in these specific cases even more effective than operation on the thyroid. When the original causative process is

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3. Bauer, Julius: Fortschritte in der Klinik der Schilddrüsenerkrankungen, Med. Klin., 1913, No. 5, p. 146.



in the intestine, particularly in the colon, there is no treatment like lavage of the colon with irrigations of 1 per cent. solutions of ichthyol. As much as 1 liter may be used in persons having a large colon and half a liter in persons with a small colon. I have also found that the *Bacillus bulgaricus* in pure liquid cultures administered for a long time reduces the tremor, as well as the headaches and insomnia.

I hope to furnish a more complete report when the cases which I still have under observation are more carefully studied. Treatments of various kinds had been administered in all three of my cases. One patient had gone through a rest-cure of ten weeks with electric, dietetic and medicinal applications. Another had been in a sanatorium for two months and had taken bromid of quinin and ergot for six weeks, with varying effects. Both of these had taken antithyroidin, but never were free from headaches, insomnia, tremors and tachycardia except when at perfect rest. Whenever they resumed their duties their symptoms returned. I kept them in bed three weeks, also, but on a meat free diet and colon irrigation and symptoms gradually abated. One patient at the date of this writing has been free from headaches, tremors, and insomnia for six months, though at times he still experiences tachycardia if he exerts himself in warm weather. A second patient has had no tachycardia that she knows of for a year, sleeps well and appears normal, excepting an occasional attack of diarrhea, which has been traceable to errors of diet. The third patient is still under observation, but is progressing so satisfactorily that, although he is a busy physician, he has had only one attack of tachycardia in nine months while attending to his professional and scientific work.

		Average Pulse
Case 1.	Before treatment .....	120
	Last six months.....	78
Case 2.	Before treatment .....	106
	After one year.....	80
Case 3.	Before treatment .....	100
	Last four months.....	74

I still advise continuance of cool needle-spray douches, strict diet, twelve hours' rest a day and one colon irrigation every six to ten days in these patients. One patient, however, has not resumed irrigation of the colon for five months and has remained sufficiently well to attend to

his work. When we remember how unpromising purely internal and physical treatment of the thyreoses has been, these results of this special therapy are sufficiently favorable to warrant a continuance of it in the special types of thyreoses in which it appears indicated.

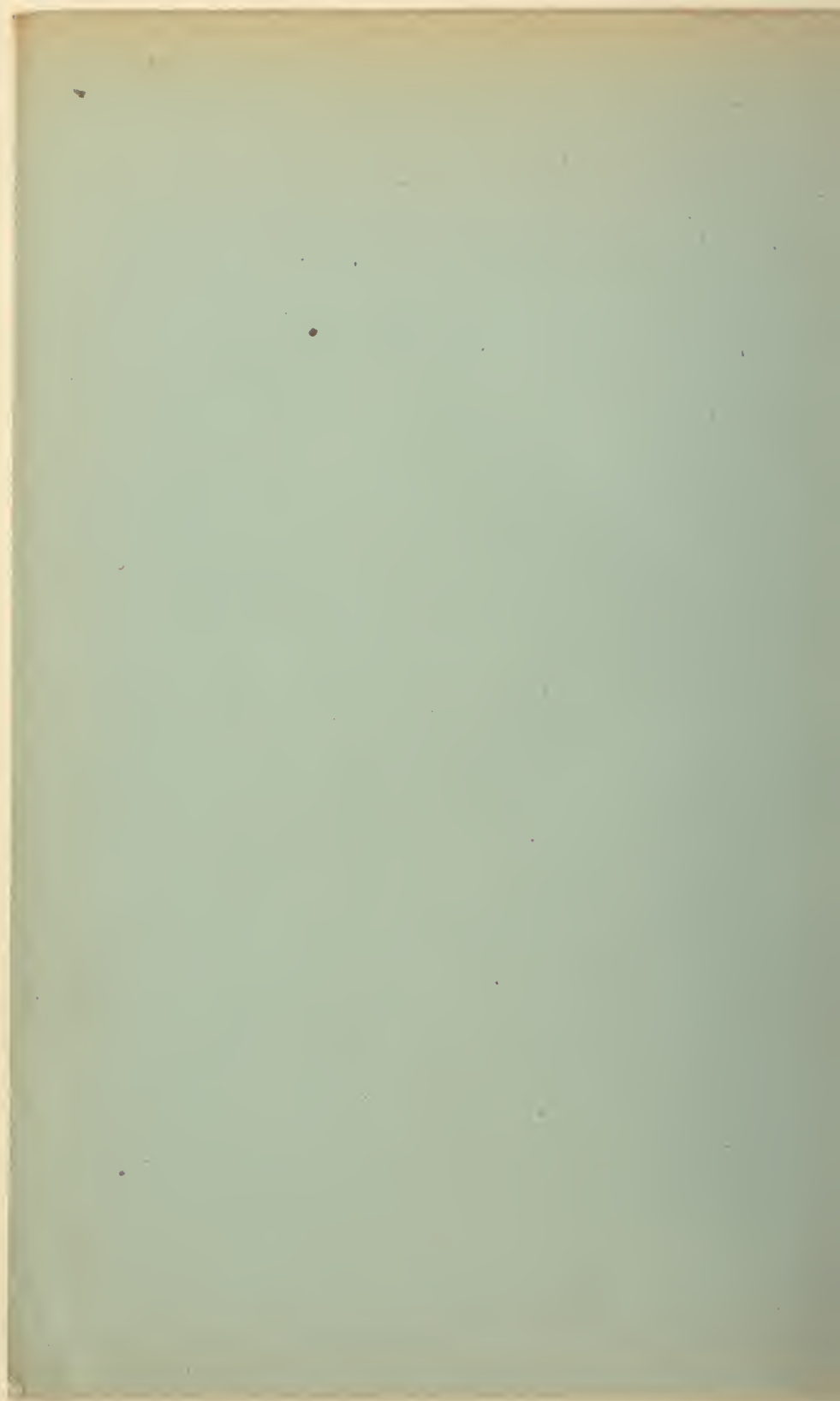
Further studies will be made to throw light on the ideas held by McCarrison, von Noorden and Sasaki, namely, to determine whether a specific microbial inhabitant of the colon is either directly or indirectly the cause of this special type of thyreoses. The chemical and bacteriologic character in all of the evacuations of these cases—I mean the study of the feces—will be reported in a future communication. But I may premise my future report by stating that no specific bacterium or protozoon has been discovered by us that enabled us to reproduce successfully the Basedowoid symptoms and signs experimentally on animals.

Read and Charles Streets.









HYPERTONICITY AND HYPO-  
TONICITY OF THE VAGUS  
AND THE SYMPATHETIC  
NERVOUS SYSTEM.

BY

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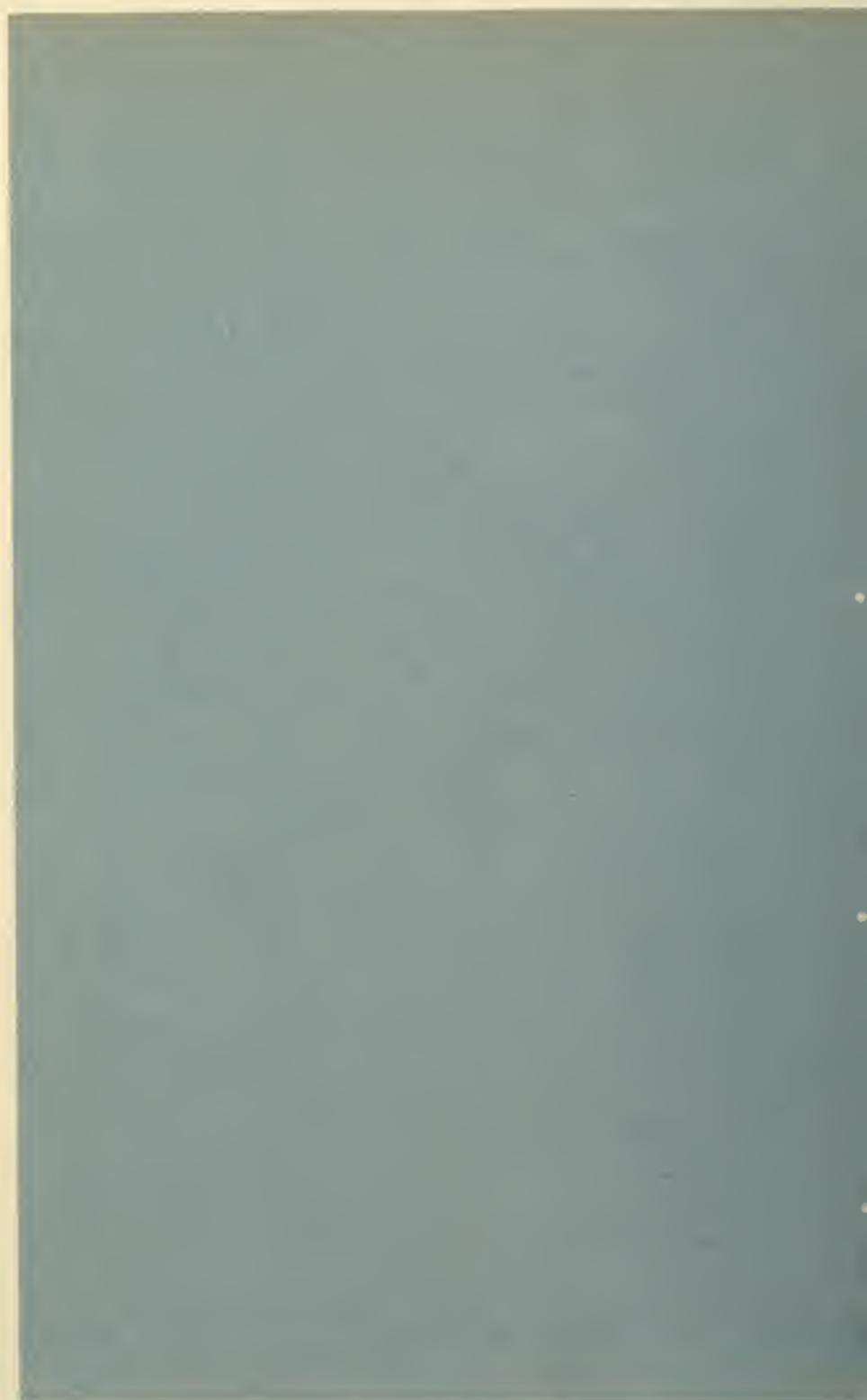
*Reprinted from the*

**New York Medical Journal**

INCORPORATING THE

**Philadelphia Medical Journal and  
The Medical News.**

*January 17, 1914.*



*Reprinted from the New York Medical Journal for  
January 17, 1914.*

## HYPERTONICITY AND HYPOTONICITY OF THE VAGUS AND THE SYMPA- THETIC NERVOUS SYSTEM.

*Neurochemical Synergism of the Normal Body and  
Its Suggestions for Physiological Therapeutics.\**

BY JOHN C. HEMMETER, M. D., PHIL. D., SC. D.,  
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The autonomic nervous system means that portion of the nervous system which appears to be self-governing, and independent of the control of nervous impulses which arise in the cells of the cerebral cortex. The neurons, which constitute the centres of the autonomic nervous system, originate the various nervous impulses which travel to the peripheral organs, such as the bloodvessels, walls of the intestines, sweat glands, etc. The fibres which convey these impulses constitute the efferent portion of the system. These central nerve cells are, however, to some extent influenced by impulses which reach them from the periphery. The fibres which convey these impulses constitute the afferent portion of the system.

### THE EFFERENT FIBRES OF THE NERVOUS SYSTEM.

The largest part of the unstriated muscle (involuntary muscle) of the body is under the control of the autonomic nervous system. As examples of the organs of the body innervated by this system, the following may be mentioned: The heart (cardioinhibitory and cardioaccelerator nerves), the bloodvessels (vasoconstrictor and vasodilator nerves),

\*Annual address by invitation of the American Therapeutic Society, held in Washington, D. C., May 5 and 6, 1913.



the stomach and intestines (visceromotor and visceroinhibitory nerves), the secreting glands, especially the gastric glands, pancreas, and liver (secretory and secretoinhibitory nerves), and the iris (pupilloconstrictor and pupillodilator). •

The nervous impulses which govern these various organs of the body arise in nerve cells situated somewhere in the central nervous system. Autonomic nerve centres are situated in the mid-brain, in the pons Varolii, in the medulla oblongata, and in the gray matter of the spinal cord. The efferent impulses leave the central nervous system by finely medullated nerve fibres, some of which travel in the cranial nerves and others in the anterior nerve roots of the spinal nerves. For the most part those nerves which convey the autonomic nerve impulses sooner or later travel to a ganglion, where the medullated nerve fibre or preganglionic fibre arborises around one or more nerve cells in this cell station. New fibres arise in these ganglion cells which are nonmedullated (postganglionic fibres). If these postganglionic fibres pass back to the neighboring spinal nerve they are termed gray rami communicantes. These fibres convey impulses to the bloodvessels (vasoconstrictor), to the sweat glands, and to the hairs of the part (pilomotor) which is supplied through that particular spinal nerve.

The nerve conveying the autonomic impulses may make cell stations in one of three regions: In the proximal lateral ganglia, which form the sympathetic nerve chain; in the more distantly placed ganglia, such as the semilunar ganglia which lie upon the large arteries of the abdomen; or in the terminal ganglia, such as are present in the walls of the viscera, namely, those in Meissner's and Auerbach's plexuses which are present in the walls of the stomach and intestine, and the ganglia present in the walls of the heart. The positions of the cell stations upon the autonomic nervous system have been demonstrated by Langley's nicotine method, which shall be described briefly in the following.

VEGETATIVE NERVOUS SYSTEM.

The so called vegetative system, whose efferent nerves supply the involuntarily active organs, is in contrast to the voluntary nerve system, histogenetically and pharmacologically. The organs which this vegetative system supplies are the glands and the organs with unstriated muscles, viz., the intestines, bloodvessels, the unstriated muscular tissue of the skin, the iris, etc. Physiologically, certain cross striped muscles should be placed on the same footing with the foregoing unstriated organs, such as the heart, cross striped muscles of the esophagus and penis, and of the iris in some animal species, for instance, birds, whose iris, in contradistinction to that of the mammals, is cross striped. The characteristic feature of the innervation of these body tissues is that their functions, although they may be partially influenced by it, are more or less independent of the central nervous system. It has, therefore, been designated by Langley, once for all, as the *autonomic nerve system*. We adopt, however, the term "vegetative nervous system" and reserve "autonomic" expressly for that part of the vegetative nerves which is not originated from the chain of sympathetic ganglia.

*Origin.* The efferent fibres of the vegetative system reach their effective organs—the muscles of the circulatory organs, of the digestive tract, of the reproductive organs, of the glands, etc.—by means of paths which emanate from peripheral nerve centres. While the fibres have their origin, indeed, in the central nervous system, it is a peculiarity of the vegetative nerves that they never proceed direct to the periphery but come, somewhere on their course, in contact with neurons, respectively, or ganglion cells.

*Sympathetic fibres.* That set of sympathetic fibres, which run out from the middle section of the spinal cord in the thoracic nerves and the first four or five lumbar nerves by means of the rami com-

municantes to the sympathetic ganglion chain, superior and inferior cervical ganglion, and also the stellate ganglion, and from them join the spinal nerves as so called gray rami communicantes, are in an anatomical, evolutionary, physiological and pharmacological sense different from the other vegetative fibres. These sympathetic nerves supply the bloodvessels, glands, and unstriped muscular organs of the whole body. They form a homogeneous part of the vegetative nervous system.

*Cranial and sacral autonomic fibres.* Almost all these organs receive still another species of vegetative nerves, which emanate partly from the brain and medulla, partly from the sacral portion of the spinal cord. We term this second part of the vegetative system the cranial and sacral autonomic nervous system. From the middle brain autonomic fibres run out which pass into the oculomotor nerve, proceed to the ciliary ganglion, and then, as short ciliary nerves, supply the sphincter of the iris and the ciliary muscle. From the medulla oblongata emanate autonomic nerves, which contain, in the chorda tympani, secretory fibres for the salivary glands and vasodilator fibres for the oral cavity. From the facial nerve and the glossopharyngeal, moreover, secretory and vasodilator fibres pass, which enter the trigeminus and supply the mucous membranes of the head (mouth, nose, pharynx). Finally, autonomic fibres pass from the medulla oblongata, which, following the path of the vagus nerve, disperse into the intestines. These are the inhibitory fibres of the heart, contractile fibres for the bronchial muscles, motor fibres for the esophagus, stomach, intestines and secretory fibres for the stomach and pancreas. This system could be designated as the cranial-bulbar, or, in brief, as the cranial-autonomic. The influence of this system is strongest at the oral end of the digestive apparatus and the adjoining parts of the head and then diminishes in scope and intensity. Near the anal end of the digestive system its influence is relieved, as it

*Hemmeter: The Vagus and the Sympathetic System.*

were, by sacral autonomic fibres, which emanate from the first sacral nerve of the spinal cord and innervate, as pelvic nerve, the anal parts of the digestive system, viz., descending colon, rectum and anus, and likewise the bladder and genital organs.

A third nervous system which controls the hollow organs, e. g., the intestine, is the one which Langley has called the "enteric system." This consists of peripheral centres working independently, which receive impulses from the central nervous system through autonomic and sympathetic connections.

*Two allied systems.* The sympathetic nerves form a physiological unity, and their terminals exhibit everywhere the same pharmacological reaction (epinephrin). According to the investigations of Langley, the cranial-bulbar and the sacral autonomic system belong together physiologically. The most striking proof of this physiological relationship is their similar behavior under the action of a certain set of poisons, to which we shall revert later. Just as the functions so also the pharmacological reactions of the cranial-sacral autonomic fibres present distinctly opposing characteristics to those of the sympathetic system, even though all vegetative nerves seem to possess about the same structure in general.

*General structure of the vegetative system.* All vegetative nerves disclose, in accordance with this similar structure, a common pharmacological reaction, the discovery of which was an important step toward the comprehension of their structure. We refer to the action of nicotine, which selects its point of attack always at some definite place in the path of all vegetative nerves. According to the general scheme of arrangement, the vegetative nerves never proceed, like the animal fibres, directly from the central nervous system to the organs they control, but the fibres, emanating from the gray substance of the central nervous system, proceed first to a ganglion. In this ganglion the cen-



tral fibre ends in a synapse which comes in contact with ganglion cells, from which the nerve fibres continue on their way to the effective organ. Hence one can designate such nerve fibres, which proceed out of the central system and before they have reached the ganglion, as preganglionic fibres, and their continuations from the ganglion cells as postganglionic fibres. At single points during the entire length of the nerve an interruption takes place, a switching from the preganglionic to the postganglionic fibre. This switching over may occur in the first ganglion which the nerve reaches, e. g., in one of the vertebral ganglia, which, corresponding to the spinal ganglia, are arranged segmentally in the sympathetic chain. Other vegetative fibres pass through one and sometimes two ganglia in their course without interruption and terminate in prevertebral ganglia that are situated in more advanced and peripheral locations, e. g., the nerve fibres of the splanchnic in the solar plexus, or the pelvic nerves in the hypogastric plexus; or they terminate in still more advanced and distal ganglia, which are imbedded directly in the organs themselves.

The vertebral ganglia, with the exception of the superior and inferior cervical ganglia, supply the vegetative structures of the skin, trunk and extremities—in fact, a variety of organs, viz., glands, bloodvessels and unstriated muscles (pilomoters) of the skin. The prevertebral ganglia supply exclusively the intestines. The stellate ganglion and the superior cervical ganglion, which can be looked upon as fused from vertebral and prevertebral ganglia, send out both intestinal and skin nerves.

*Similar reaction from nicotine.* In whatever region the place of the termination of the central fibre and its switching over may be found, and no matter which function the postganglionic fibre may possess, whether as motor, inhibitory or secretory, the place of the switching over is paralyzed by nicotine after a preliminary period of excitation. *This*

is a general law. To be sure, the various ganglia exhibit different degrees of sensitiveness. There is much variation in this matter in the case of different animal species, e. g., nicotine is far less effective on the intermediate ganglion 'tween stations of a dog than in the case of the cat and rabbit.

Langley employed nicotine for the local poisoning of the separate exposed ganglia by means of painting them with a diluted 0.5 per cent. solution, so as to determine the question whether an efferent vegetative nerve fibre passes a certain ganglion without communication or whether at the painted locality a switching over in the line of conduction has taken place. If the excitation of a nerve centrally from the ganglion has the same effect after the application of the poison as before its use, then the nerve fibre passes uninterruptedly through the ganglion; if, on the other hand, there is no effect after the use of the poison, then the fibre terminates in the ganglion and the postganglionic fibre originates there. By means of this method Langley demonstrated the interruption of numerous sympathetic and cranial-sacral nerves in the various corresponding vertebral and prevertebral ganglia. One example may illustrate this. The excitation of the cervical sympathetic below the stellate ganglion causes contraction of the bloodvessels of the upper extremity and simultaneously, also, dilatation of the pupils, widening of the lids, and a change of the width of the bloodvessels and of the secretive functions of the mucous membranes of the head. After the application of nicotine to the stellate ganglion, the excitation of the cervical sympathetic has no effect on the width of the blood vessels of the extremity, but the phenomena on the eye and the mucous membranes of the head remain the same. Hence, the vascular nerves of the extremity stand in communication with nerve cells in the stellate ganglia, while the nerve fibres of the pupils and the mucous membranes of the head pass through this ganglion and find their intermediate

stations only when they reach the cervical ganglia. If nicotine is injected into the circulation, then the excitation of all preganglionic fibres is ineffective, while, on the other hand, the excitation of the post-ganglionic fibres produces all the phenomena of the nerve in question. Hence the nerve fibres and peripheral terminals remain subject to excitation, only the intermediate stations in the ganglia—those we have designated as the points of switching over—being poisoned by nicotine.

RECIPROCAL FUNCTIONS OF THE TWO SYSTEMS.

The action of the nicotine extends, also, to all ganglia of the vegetative system, irrespective of the fact as to whether they are of sympathetic origin or belong to the autonomic system. In other respects these two groups of vegetative nerves exhibit opposing features in their conduct, both physiologically and pharmacologically. It is of great importance that most organs possess a twofold innervation, on the one hand from the sympathetic system and on the other from the related, or corresponding, cranial or sacral systems. Almost everywhere where the organs possess a twofold innervation, the one is antagonistic to the other; to wit, the stimulation of the sympathetic fibre produces an effect just opposite to that of the autonomic fibre. For instance, if the sympathetic splanchnic nerve checks the movements of the intestine, then the autonomic fibres of the vagus excite the upper sections of the intestine, and the sacral fibres of the pelvic nerve the lower sections. If the sympathetic nerve affects the dilator of the iris, then the autonomic branch of the oculomotor exerts an influence on the antagonistic sphincter of the iris. The heart checking action of the vagus fibres is opposed by the accelerator of the sympathetic. In brief, nearly all organs, which are known to possess an innervation from both these systems, are affected by them in an antagonistic manner. A group of organs, viz., the blood vessels and glands of the skin of the trunk and

extremities, are of course, so far as we know today, only innervated by the sympathetic system.

*Epinephrine, a sympathetic poison.* The difference in the physiological conduct of the two vegetative systems is also exhibited in their pharmacological reaction. There is a group of poisons which affects only the sympathetic and one which affects all the various autonomic terminals. Thus, epinephrine (from the adrenal bodies) excites the nerve endings everywhere where they are terminals of sympathetics, that is to say, the action on the organs is always the same as the excitation of the corresponding sympathetic fibres. Epinephrine, on account of its action on the nerve terminals of sympathetic fibres, produces constriction in all vascular territories. It superinduces an enforcement and acceleration in the rapidity and strength of the heart beat, just like the excitation of the accelerator. It causes enlargement of the pupils, like the cervical sympathetic, and increases the secretion of the salivary glands, to the extent that they can be induced to action through the sympathetic nerves. At such places, however, where the sympathetic fibres display an inhibitory influence, e. g., on tissues in the stomach and intestine, or on the bladder, epinephrine will not cause an excitation, but a checking influence. Especially striking are those cases in which the stimulation of the sympathetic fibres in one species of animal causes contraction, but in another species of animal produces inhibition of the same organ, as, for example, in the case of the bladder. Epinephrine always acts just as the stimulation of the sympathetic would act (Elliott, *Journal of Physiology*, xxxii, 1905). We can say, therefore, that the excitation or inhibitive effect of epinephrine selects only those terminations of the vegetative nervous system which belong to the sympathetic system.

*Effects of epinephrine on various tissues are analogous to the effects of stimulating the sym-*



*pathetic nerves that supply those tissues:* 1. In all bloodvessels epinephrine causes constriction. 2. As we have seen in previous experiments, it increases the contractile force of the heart. 3. The pupil is dilated (mydriasis). 4. The muscle of the intestine in all mammalia is inhibited, with the single exception of the ileocecal sphincter. 5. The stomach in mammals is relaxed, but in the frog it is brought to contraction, so that both of these effects correspond with those obtained in stimulating the sympathetic nerve going to those tissues, in the respective species. 6. The effect of stimulation of the sympathetic nerve for the bladder and uterus varies in different animals; but no matter what this effect is, a similar one is produced by the application of epinephrine.

*Ergotoxin.* In ergot, Dale discovered another poison, ergotoxin, which makes a still closer selection of nerve terminals of the sympathetic system, in that it only paralyzes those terminals of the fibres which exert a stimulating effect, but does not affect those which cause inhibition. After large doses of ergotoxin, the stimulation of the vasoconstrictors causes no narrowing of bloodvessels. The accelerator nerves are not affected, but the inhibitive effects of the splanchnic on the intestine, or of the sympathetic nerves in case they inhibit the bladder, remain intact in their function.

*Poisons for the autonômic terminals.* Adrenalin has no effect on the sacral autonomic terminals, but there is another group of poisons which attacks just this end apparatus and which, with one exception, exerts no effect on the sympathetic nervous system. The principal members of this group are, on the one hand, atropine, and on the other, muscarine, pilocarpine, physostigmine, and also choline. Among these, muscarine stimulates the terminals of the autonomic fibres and atropine paralyzes these terminals. The poisons of the muscarine group bring about, accordingly, contraction of the pupils; atropine counteracts the influence of the autonomic

motor oculi, and hence causes pupil enlargement. Muscarine affects the heart similarly to the stimulation of the vagus; atropine paralyzes the effect of the vagus, and thus permits the quickening influences of the sympathetic fibres to gain supremacy. Muscarine causes spastic contraction of the bronchial muscles; atropine relieves the spasm. Muscarine and pilocarpine cause severe contractions of the muscles of the stomach and intestine and of unstriated muscles of other organs; atropine in certain doses relieves the tension of these muscles. Muscarine and pilocarpine cause secretion in all glands; atropine arrests this. But these poisons attack, also, the glands of the skin, although an innervation of the skin glands by autonomic fibres, i. e., nonsympathetic fibres, is as yet unknown. One is almost tempted to believe that this exception is only an apparent one, and that an explanation will be found on further investigation. Incidentally, let it be said that the points of attack of the poisons here considered are not fully known. This much has been determined, however, that all of them attack the end apparatus of autonomic nerves, and the various end apparatus of this system are thereby marked as belonging together by this common pharmacological behavior.

*Reactions of poisons on autonomic centres.* Similar pharmacological, i. e., chemical reaction, points to similar chemical structure. It will be necessary, therefore, to accept as a fact the common structure of all sympathetic end apparatus and likewise, in the case of the autonomic end apparatus among themselves. But also in their points of origin, located in the central nervous system, these two great groups seem to differ and to individualize in their peculiar chemical reactions. Picrotoxine, which produces a number of interesting effects not to be considered here, stimulates all cranial and sacral autonomic nerves, motor oculi, chorda, vagus, pelvic nerves, and what is more, not at their end apparatus but exclusively at the central point, or

*Hemmeter: The Vagus and the Sympathetic System.*

origin. The autonomic centres exhibit, hence, all the same chemical reactions. This same statement cannot be made of the sympathetic central apparatus, for up to the present only a few data exist pointing in that direction.

*Variety of poison stimulations of the vegetative system.* Nicotine, then, attacks the ganglia of the entire vegetative system, epinephrine only the terminal of the sympathetic fibres, the atropine-muscarine group specially the terminals of autonomic nerves. In addition to the poisons referred to, there are many other substances which act on special sections of the vegetative nervous system. Since all organs which have a twofold innervation will be affected in the same manner by the stimulation of the one system and the paralysis of the other, the same changes of functions can be brought about from different points of attack; thus, enlargement of the pupils will occur through stimulation of the sympathetic nerve terminals in the iris by the use of adrenalin, as by paralysis of the terminal of the motor oculi through atropine. Thus the heart beats rapidly by stimulation of the terminals of the accelerators through large doses of caffeine, as through paralysis of the vagus through atropine. It will appear that uncommonly numerous and complicated effects of poisons are therefore possible on the vegetative nervous system.

AN EXAMINATION OF THE FUNCTIONS OF THE  
VEGETATIVE NERVOUS SYSTEM.

Since the pharmacodynamic examination of the functions of the vegetative nervous system by Eppinger and Hess has been developed for clinical purposes, a series of important results may yield to further investigation. The various and diverse symptomatology of functional nerve disturbances appeared at last ready to be systematized and the point of view which was to determine the classification was derived from knowledge obtained through physiology and pharmacol-

ogy. Eppinger and Hess, in particular, attempted to outline a disease, "vagotony," and differentiate it from the manifold mental disorders. The two authors believed themselves justified, on the basis of clinical considerations and the results of their investigations of the functions of the vegetative nervous system, in defining a functional derangement of the autonomic nervous system, or extended vagus territory. On the one hand, all symptoms of such patients apparently could be interpreted as caused by the state of irritability of the autonomic nervous system; on the other hand, Eppinger and Hess noticed that pilocarpine and atropine were very effective in the case of such patients, while epinephrine exerted no action. Likewise, however, just as there are persons who respond relatively not at all to epinephrine, but strongly to atropine and pilocarpine, there are also persons who, on the application of epinephrine, exhibit phenomena of strong stimulation of the sympathicus, but are not susceptible to pilocarpine and atropine. "Data to the effect that persons to whom we administered doses of atropine and pilocarpine and also of epinephrine had responded vigorously to the former two and in the same measure to the third, are completely wanting" (Eppinger and Hess). Thus these two able authors were led to assume two antipodal systems of diseases, or dispositions, the vagotonic and the sympathicotonic dispositions, respectively diseases.

The Eppinger-Hess point of view, however, soon had to undergo modifications owing to data which had come to hand in the meantime. The justification of placing vagotony and sympathicotony in opposition to each other seemed doubtful as soon as it became evident that in some cases pilocarpine and atropine, as well as epinephrine, produced strong reaction in the same person. And Eppinger and Hess, in conjunction with Potzl, were themselves the first to obtain data of this character from certain neurasthenics. In the case of manic depressive insanity they observed regularly, along with the change of



the various stages of the disease, fluctuations in the tonus of the vegetative nervous system, these fluctuations being the same for both systems. Falta, Newburgh and Nobel noticed in the case of diabetic patients afflicted with multiple sclerosis and a bronchial asthma with tetany, strong response to pilocarpine, as well as to epinephrine, and Falta was able to demonstrate in conjunction with Kahn that this phenomenon was normal in the case of tetany. More recently Petren and Thorling have made investigations with "a rather heterogeneous clinical material" and succeeded in refuting the Eppinger-Hess assumption that epinephrine and pilocarpine cannot produce a reaction on one and the same individual. On the other hand, they admit that cases of pronounced vagotony and sympathicotony, respectively, do exist, and they find with ulcer of the stomach, particularly, relatively very often a strong "vagotonus." Petren and Thorling retain this term, although they expressly assert that in all probability the whole matter is not concerned with an increased tonus of the autonomic or an abnormally diminished tonus of the sympathetic system, respectively, but rather with the fact that frequently one and the same individual is strongly susceptible to pilocarpine as well as epinephrine, which is hardly to be explained otherwise than through the assumption of greater irritability to stimuli of autonomic, as well as of the sympathetic nervous system. In opposition to the assumption of an increase in the tonus, and supporting that of greater irritability to stimuli, these two concepts are to be sharply differentiated. Petren and Thorling offer as additional proof that they, in contradistinction to Eppinger and Hess, could discover no parallel relation in this matter of sensitiveness to pilocarpine and atropine. If a strong pilocarpine action was assignable to an increased tonus in the vagus system, then a strong atropine action could be expected to result from the elimination of this nerve system with this increased tonus. But when we assume an abnormal irritabil-

ity, instead of increase of tonus, it is easy to see that, notwithstanding the strong reaction to pilocarpine, the nerve system in a state of increased irritability might yet be resistant to the paralyzing action of atropine.<sup>1</sup>

A number of casual observations, which affected the theoretic foundation of the whole question and explained clearly many phenomena hitherto little or not at all heeded, induced Bauer, even before he could possibly have known anything of the investigations of the Swedish scientists, to make an examination of the functions of the vegetative nervous system, using clinical material of the most varied character, not the result of any particular selection, but in greater part exhibiting neuropathic phenomena.

In addition to the pharmacodynamic methods of testing functions, there exists, as is well known, a few mechanical or physical methods which can be applied to our examinations and combined with pharmacodynamic methods. These are the tests for: 1. Dermographism; 2, irregular respiratory pulse; and, 3, the Aschner reflex, or reflex by pressure on the optic bulb influencing the vagus. Further physical methods, such as the Czermak vagus pressure test or the Erben phenomenon, we shall not consider here, because they were not employed consistently in our investigations.

*Dermographismus* has been regarded for some time as a neuropathic stigma. Polonsky devoted much attention to this symptom recently. He discovered the existence of "vasomotor afterblushing" in the case of all the patients examined by him to the number of 116 from the psychiatric and nerve clinic of the Berlin Charité. Of these, sixty-seven suffered from functional, and forty-nine from organic neurotic affections. Polonsky interprets the vasomotor afterblushing as pathognomonic, as an affection of the central nervous system, and suggests that

<sup>1</sup>For new physiological conceptions of Tonus, see Starling's *Physiology*, pp. 377-380.

it is to be regarded as a general indication of the fact that the system has lost its normal condition of equilibrium, or is to be regarded as an indisposition, but not a characteristic feature of special disorders of this central nervous system. Everything likely to affect the organism, such as psychic influences, alcohol, coffee, abuse of nicotine, menstruation, pregnancy, etc., has a tendency, according to Polonsky, to increase this vasomotor afterblushing. Springtime is also supposed to superinduce it.

More important than the investigations of Polonsky is the peculiar reaction of certain individuals on vigorous rubbing of the skin, to which attention was called by Hess and Königstein. This phenomenon, to which Hess and Königstein have applied the term "perverse reaction," consists in that these individuals, in contradistinction to almost all others, do not respond with vasodilatation, but with vasoconstriction, to the mechanical skin stimulation, and simultaneously show a stimulating reaction of their pilomotor nerves. I was in the habit of terming this phenomenon, before the publication of the Hess-Königstein work, as "white" or "goose skin" dermatographism. Hess and Königstein interpret as perverse reaction, moreover, that seen when individuals respond with anemia instead of hyperemia to heat, and by redness instead of pallor to cold. Such people have frequently a pale facial color, and become still paler under the action of psychic influences, when others would respond with blushing.

H. E. Hering, more than all others, has pointed out the practicability, for purposes of functional investigations, of the cardiac vagi, the respiratory arrhythmia of the pulse. As is well known, the irregular respiratory pulse consists of an increased acceleration of the heartbeat and the decrease in size of the pulse waves during inhalation, but during expiration the pulse becomes less frequent and larger. A number of isolated references to this form of pulse arrhythmia were already extant in the literature, when Lommel devoted especial attention

to the matter and could demonstrate the nervous origin of the pulse arrhythmia and its dependence on highly increased irritability of the vagus. With animals (the dog) when the vagi have been severed, or atropine has been administered, likewise in the case of fever (vagus paralysis), the previously existing respiratory arrhythmia disappears. Even when the thorax of the animal has been opened wide, and hence no stretching or any other mechanical agency is applied to the breathing apparatus, the respiratory pulse arrhythmia remains. It is, hence, not the result of respiratory mechanical conditions (pressure variations) of the thorax and lesser circulation. On the basis of further considerations, Lommel believed that "an excessive sensitiveness of the cardioinhibitory vagus centre" was the cause of the respiratory pulse arrhythmia; to which must be added that the normal respiratory influences change the existing degree of irritability of the vagoinhibitory centre to a marked degree. According to Hering, respiratory arrhythmia is only, then, pathological when it becomes strongly noticeable even with very light respiration. A strongly accentuated form of it seems to be normal with young individuals. The "infantile type" of heart irregularity, so defined by Mackenzie, is, according to Hering, the irregular respiratory pulse. Lommel and Hering observed the respiratory pulse arrhythmia especially in persons who were recovering from febrile diseases, those suffering from neurosis and from cerebral diseases with stimulation of the vagus centre. The irregular respiratory pulse in the case of heart disorders is not causally related to the latter. Hamburger regards the irregular respiratory pulse as a characteristic symptom of nervous children. The existence of an irregular respiratory pulse proves, according to Hering, the presence of a tonus of the heart inhibitory fibres. Also, the very noticeable diminution of the number of heart beats after holding the breath for some time is supposed to demonstrate the functioning of the heart vagi.



Hering regards the determination of the irregular respiratory pulse as a more valuable functional test of the heart vagi than the Dehio atropine test—pulse rate increase after atropine—because failure of this atropine test could depend upon a certain degree of immunity to atropine. This fact, emphasized by Hering, is being corroborated by the new investigations of Fleischmann with reference to the different degree of detoxication of atropine by blood serum.

The third mechanical method which can be recommended for examination of the functions of the vegetative nervous system is the *bulbus pressure phenomenon*, described by B. Aschner, who, starting from the observation of von Wagner-Yauregg that persons affected by stupor can be brought back to consciousness in a surprising manner, if only for a short period, through a pressure on the optic bulbs, tried to revive persons that were in deep stupor, the result of narcotics, by the same method. Along with flushing of the face, some retching movements, deep inhalation, and opening of the eyes, Aschner noticed in the case of his patients a cessation of the pulse with consequent bradycardia. Breathing, also, became slower and deeper. Corresponding experiments on animals showed without doubt that this was a result of a reflex, the afferent path of which was formed by the first branch of the trigeminus. Pressure on a branch of the trigeminus in the eye cavity, after removal of the bulbus, also produced the vagus reflex; not only the first branch of the trigeminus, but also the second and third can form the centripetal joint of the reflex curve. Through mechanical or electric stimulation of the third branch, similarly, expiratory cessation of respiration and pulse diminution, respectively, cessation of heart beat can be brought about. With regard to the second branch, Kratschmer had already observed, in 1870, the same phenomena by means of stimulation of the nasal mucous membrane with tobacco smoke. According to Aschner, the inhibitory action of the reflex affects the respiration

most prominently in the rabbit, and the heart in the case of a human being (nonsmoker) and dog.

Eppinger and Hess described the development of this Aschner phenomenon in the case of several of their vagotonic patients, and remarked, incidentally, that the phenomenon can frequently be demonstrated only by determination of the pulse curves. Moreover, Eppinger and Hess also produced very pronounced bradycardia in certain cases by stimulation of the nasal mucous membrane with ammonia vapors. Miloslavich followed up the development of the Aschner reflex systematically with a series of heart neuroses, and determined that at times very remarkably intensive bradycardia, sometimes a reduction of from eight to ten beats a minute in the pulse, followed on bulbous pressure. In other cases, however, the pulse remained the same. Miloslavich, in agreement with Eppinger, explains this behavior from the fact that there are some heart neuroses that respond to vagus stimulation and others to sympathetic stimulation. In addition, Miloslavich found this reflex regularly present in epileptic attacks, while it was always absent in hysteria. In the case of deep alcoholic intoxication this reflex is also present. The reflex from the eye to the heart makes, therefore, as Miloslavich states, no especial impression on normal persons in a state of wakefulness, but does so with a vagotonic person, who is under the influence of a narcotic, and in all other forms of unconsciousness, coma, etc.

The functions of the vegetative nervous system have been tested by Eppinger and Hess (*Zeitschrift für klinische Medizin*, 67 und 68; also *Die Vagotonie. Sammlung klinischer Abhandlungen*, herausgegeben von Noorden, 9 und 10) and by the authorities quoted in the preceding, and especially by Julius Bauer, who was working at the medical clinic of the University of Innsbruck. The results of these various authors do not permit of any dogmatic or categorical conclusions concerning the re-

lation of the autonomic to the sympathetic nervous system. The tests were made by the physical methods which I have described, namely, counting the pulse during the pressure upon the eye bulbs, the so called Aschner reflex, which is an inhibition of the vagus by pressure on the first branch of the trigeminus nerve. In this connection I may state that the second and third branches of the trigeminus may also serve as afferent paths of conduction to the vagoinhibitory centre. By stimulation of these branches, slowing of the pulse may be brought about in susceptible individuals. Kratschmer, quoted according to Aschner, described slowing of the pulse by stimulation of the nasal mucosa with tobacco, and I have personally observed in human beings who were not addicted to the use of tobacco and who were very susceptible to the smoke, that a slowing of the pulse was noticed when they were compelled to draw in even the diluted smoke of tobacco. Eppinger and Hess (*loco citato*) effected pronounced slowing of the pulse by irritation of the nasal mucosa with fumes of ammonia. This may explain the beneficial action of the various ammonia smelling salts when applied in cases of fainting with rapid heart. I am personally studying a male patient at present in whom pressure upon the eye bulb to a moderate degree will completely arrest the heart for five or six beats. It will then recover, but as long as the pressure upon the eye lasts, will not exceed forty beats a minute, the patient's normal heart rate being sixty-eight. Any influence of the eye bulb pressure upon the heart rate is pathological. It is never observed with perfectly normal individuals. If it, therefore, can be produced in a human being, it is justifiable to conclude that the person is in a vagotonic condition. It should be added that conditions of narcosis, unconsciousness, alcoholism, and coma should be excluded, and such states are not fit conditions for this experiment.

In addition to these physical methods of investi-

gation, patients were studied by injecting chemical substances under the skin in order to study whether the physiological effects could be brought out in an exaggerated or in a diminished manner according to the state of the patient, particularly according to the vagotonic or sympathicotonic state. I have repeated these pharmacological studies on a number of patients, which I shall detail under a special heading, and used the tests employed by Bauer (*loco citato*), Petren und Thorling (*Zeitschrift für klinische Medizin*, lxxiii, 1 und 2, 1911). We injected subcutaneously the following test chemicals in the doses assigned: Pilocarpine, 0.007 gram up to 0.01 gram; epinephrine, 0.0007 gram, on the average 0.0005 gram. I also used atropine sulphate in doses of 0.0005 gram. Eppinger, Hess, and Potzl (*Wiener klinische Wochenschrift*, 1910) used 0.001 gram of pilocarpine to the kilogram weight of human being, and of atropine and epinephrine they used 0.0001 gram to the kilogram; which are, in my opinion, enormous doses and entirely unnecessary for the elicitation of the physiological effects of the drug. When epinephrine was given, the patient was ordered to take 100 grams of dextrose two hours before the injection, in order to test whether the assertions of Eppinger, Hess, and Potzl were correct regarding the excretion of glucose in the urine under these doses of epinephrine. With the doses of epinephrine that were used by me, namely, about 0.005 gram, I have not in a single instance observed glycosuria, and consider the production of this condition as an indication that too much epinephrine has been given. A pronounced epinephrine effect on the organism can be produced long before doses are reached which will cause the appearance of glucose in the urine. It is, in my opinion, therefore, not justifiable to push epinephrine to the glycosuria point. In connection with this subject, I may call attention to the possibility that the epinephrine injections for the purpose of testing the functional



power of the kidneys as regards the threshold of excretion for glucose always require such large doses that the patient or animal is, in my opinion, in a distinctly pathological condition of metabolism when this glucose excretion sets in.

I also made experiments on animals and human beings with ergotoxin, and used it on three cases of Basedow's disease in which I had, by exclusion, reached the tentative opinion that the tachycardia was due to excessive stimulation of the accelerator nerves (sympathetic) on the heart. As is well known, ergotoxin makes a very narrow selection of the nerve terminals of the sympathetic system. It paralyzes the terminals of those special fibres that exert an excitatory effect. It has no influence on the inhibitory sympathetic fibres. For instance, after large doses of ergotoxin stimulation of the vasoconstrictors can no longer produce narrowing of bloodvessels; the accelerator nerves of the heart are no longer effective, but the inhibitory effects of the splanchnic on the intestine or of the sympathetic nerves on the bladder, in those animals in which these nerves do inhibit the bladder, continue to exist. In these three cases of Basedow's disease with pronounced tachycardia, ergotoxin actually did produce slowing of the pulse, and in such small doses that no other, especially no unpleasant pharmacological effects were noticed. If any one of these chemical substances was given to the patient, the rate of the pulse and respiration was recorded; the blood pressure was taken by the Tycos sphygmomanometer; the temperature by a one minute thermometer in the axilla; also, a record of the testing by the Aschner reflex, the dermographism, and the respiratory pulse arrhythmia. The urine was examined one hour before and three hours after the injection. The condition of the sweating and salivation was noticed in all instances. These substances are all poisons of one sort or another, and should be used with doses rather smaller than larger than I have indicated, because it will be found that there

are individuals of extreme sensitiveness to any one of these chemical substances, and the chief aim should be, after the consent of the patient has been obtained, not to produce any physical discomfort. Especially is care necessary with atropine, pilocarpine, and epinephrine.

In looking over the results obtained we note that there are effects of a pharmacodynamic nature discovered in testing the sympathetic, as well as the autonomic nervous system that cannot be classified in the scheme of Eppinger and Hess. Especially must their dogmatic statement be corrected that pilocarpine stimulates and atropine paralyzes all of those autonomic nerve fibres whose function is promotion of an action. There were known exceptions to these statements even before the work of Eppinger and Hess was published. These are especially the effect of pilocarpine and atropine on the sweat glands, which are innervated by sympathetic fibres, and the effect on the inhibitory vagus fibres on the heart by pilocarpine and atropine. Bauer (*loco citato*) states that the most frequent effect of epinephrine, namely, the acceleration of respiration, the tremor, the augmentation of the Aschner reflex, and the respiratory arrhythmia, are not caused by excitation of the sympathetic, but by excitation of the subcortical brain centres, and the reasons which he assigns (pp. 88 and 89, *locus citatus*) are most convincing. The epinephrine tremor closely resembles the tremor of Basedow's or Graves's disease, and can be produced by the injection of 0.0015 milligram of epinephrine in some individuals. Lewandowsky (*Archiv für Anatomie und Physiologie*, p. 360, 1899. *Zeitschrift für die gesammte Neurologie und Psychiatrie*, Ref. ii, p. 824, 1910, und 4, 1911) makes the following statement: "It is certain that most kinds of tremor are conditioned centrally, though in rare instances they may be of peripheral origin." Kraus, Friedenthal, Brokin, and Trendelenburg assert that epinephrinemia is constantly present in Basedow's dis-

ease, and Kraus has brought forward convincing proof that other blood glands beside the thyroid are pathologically deranged in Basedow's disease. It is of importance to mention this in connection with the preceding remarks. These facts, taken together with the general augmentation of the reflex excitability and the excitatory effect on the central and peripheral vagus (Verworn, Amberg, Langley, and Neujean) and the rarely observed provocation of sweating by epinephrine are observations which considerably reduce the so called elective affinity of epinephrine. We have then observed that subcutaneous injections of pilocarpine, instead of causing slowing of the pulse, may, in man, cause acceleration; for it is known that pilocarpine can reduce the facility of response of the heart to vagus stimulation. Concerning atropine, it has been observed by Bauer that, instead of quickening the pulse, it may cause slowing, and it has been furthermore observed that in rabbits pilocarpine may produce glycosuria and polyuria.

Biological laws should have no genuine exceptions. As long as exceptions exist, every one has the right to regard all schematizing as unproven that neglects these exceptions, and such schemes as are impediments to real progress. Even though a functional antagonism between so called sympathetic and the remaining autonomous nerve systems exists, and although embryologically sympathetic and autonomous systems can be separated, nevertheless the anatomicoembryological and physiological systems are not entirely identical with the pharmacological.

#### ORGAN NEUROSES.

The thyroid can be influenced by nerve fibres in the superior laryngeal nerves (Katzenstein, Exner, H. Wiesner, and especially Asher, and Flack). Moreover, these special fibres are of sympathetic origin. We now are learning with growing certainty that we can have secondary secretory neu-

roses of the thyroid simulating Basedow's disease, but due to a primary disease of these sympathetic secretory fibres. The thyroid is just as well dependent upon and controlled by the neural system as the salivary, or any other glands; therefore we have a right to believe that there are thyroid neuroses just as there are gastric neuroses. This is made all the more probable by the fact that clinical cases with all the phenomena of Basedow's or of Graves's disease are found that were not relieved by thyroidectomy, and where parts of the removed thyroid were found normal—no hyperplasia of secreting vesicles, no liquefaction of colloid material, and no small round cell infiltration.

*Adrenal neuroses.* The splanchnic nerves have been recognized as containing the secretory fibres for the suprarenal bodies (Dreyer, Biedl, Tschoboksarow, Asher). Even the hypophysis appears to function under nerve control. We shall have to expand the conception of thyroid gland neuroses to a more comprehensive conception of *ductless or blood gland neuroses*; whereby I mean all those conditions where, with a manifest existence of general overexcitability and overirritability of the vegetative nervous system, the organs of effect or response to this overirritable nerve system are represented by certain ductless, or so called blood glands. These glands with internal secretion answer to the increased innervation impulses by an increased secretion. We are dealing with blood or ductless gland neuroses, when the overexcitability of the vegetative nerve system finds expression in augmented function of certain ductless glands. If it is now recalled that the principal effect of the secretion of the best studied of these glands with internal secretion is one of stimulation (for the word *hormone* means to excite or stimulate—a designation given by Bayliss and Starling), it must become impressively apparent that an overirritable nerve system is being successively made still more irritable by the products of its own overactivity. (*Das ist*



*der Fluch der bösen That, dass Sie fortzeugend Böses muss gebären.* Schiller.) And in the new conception of ductless gland neuroses due to hyperirritable vegetative nerves acting on blood glands as their organs of response, a vague old idea is reborn in more precise physiological garb, namely, that of the "vicious circle"—the overirritable sympathetic nerves whipping on to overwork the very organs whose secretion will, in turn, prevent these identical nerves from ever coming to rest. Verily, the surgeon is justified in severing the cervical sympathetic to the thyroid in hyperthyroidosis, rather than performing thyroidectomy, for only a destruction of a link in the overactive chain of neurochemical events can destroy the "vicious circle."

The glands with internal secretion regulate the tonus of the nervous system and of the muscle fibres in the walls of the bloodvessels. This nerve and vascular tonus, together with the entire blood gland ensemble and the general composition of lymph and blood plasma resulting therefrom, are the most important factors in that which has been called the "constitution of the organism." The blood and neurosis command a specific and peculiar classification, therefore, in contradistinction to the remaining organ neuroses. For the internal secretory or blood gland neuroses furnish the fuel for their self destruction, and long before they are recognizable as manifest neuroses, they secretly furnish the transition between constitution and disease, for what may at one time impress the clinician as a constitutional peculiarity may at another, when a quantitatively increased measure of automatic mutual nerve, gland, and chemical derangement has developed, represent a grave disease.

The elective affinity of the chemical substances mentioned for certain parts of the vegetative nervous system has been designated by the term "tropism." I should prefer the more precise term of "pharmacotropism"; but in making this conclusion as defined in the preceding, namely, that

pilocarpine excites and atropine inhibits all autonomic nerve fibres whose function is the furthering of an action, etc., etc., the respective authors have neglected the condition of the so called organ of response, that is, its ability to react and the degree to which it will answer to the stimulation of nerve and chemical substances. It is a curious fact that patients who already have an organic disease of the stomach will answer more readily to chemicals that excite the secretion and motions of the stomach than normal individuals. The same can be said of the heart, the kidney, the skin, the internal secretory glands, and the general nervous system. Certain constitutional types of human beings, therefore, will react to epinephrine, for instance, preeminently with tremor because their neuromuscular system is already unbalanced. Others will react with acceleration of the pulse, because their neurocardiac apparatus is most susceptible, and still others will answer with increased blood pressure, or even excretion of glucose because their vasomotor apparatus and their metabolism and renal apparatus are most sensitive, or perhaps already damaged. In the same way there may be different kinds of effects of pilocarpine. Indeed, I can agree with Bauer, Petren, and Thorling that most human beings react as well to pilocarpine as they do to epinephrine. The phenomena which are interpreted as due to increased vagotonus—namely, slow heart, increased gastric and esophageal peristalsis, inclination to sweating and bronchial asthma, eosinophilia, and excess of hydrochloric acid—are found often in human beings who react as well to epinephrine as they do to pilocarpine. On the other hand, there are human beings who have absolutely no secretion of hydrochloric acid, who at times show alimentary glycosuria—in short, such as Eppinger and Hess would designate as sympathicotonic human beings that react most intensely to pilocarpine. Therefore, as I have already pointed out in my publication on splanchnoptosis (*Interstate Medical Journal*, xix,

No. 3, 1912), the physiological and pathological antagonism of two human conditions called *vagotomie* and *sympathicotomie* is so exceedingly difficult of execution in practice that it cannot serve as a means of clearing up our insight into the workings of the nerves upon glands, muscles, bloodvessels, organs, etc. The increased excitability of various human beings to epinephrine, atropine, pilocarpine, ergotoxine is more an indication that the entire vegetative nervous system—the sympathetic as well as the autonomous—is in a state of morbidly increased irritability. There are two fundamental concepts which we must bear in mind in interpreting these complex pharmacotropisms: First, that there is a diffuse dissociation of the individual effects of the neurotropic substances; secondly, that when the tonic innervation, the increased excitability of the vegetative nervous system has been found to exist, it need not come to expression in all organs of response with the same intensity, but the most varied combinations, phenomena, and degrees of effect may be observed in these organs. In other words, the various organs of effect in single individuals react in a different manner to the same stimulus. This may be explained in a variety of ways. The so called antagonistic tonus (the reciprocal or contrary innervation of S. J. Meltzer; see, also, Sherrington) is of varying intensity. It is, therefore, also plausible that this condition of reciprocal or contrary innervation, or what we could call antagonistic tonus, may be physiological as long as it serves the purposes of the entire organism in a beneficial manner. It is pathological as soon as one or other tonus is so exaggerated that the common welfare of one or other organ is in danger, and this is exactly what hypertonus of the vagus and sympathetic can lead to. Increased excitability of the vegetative nervous system may give origin to organ neuroses. These may be brought about by two conditions—either the overexcitability of the nerves supplying the organ,

or a morbid condition in the organ itself rendering it more reactive. In this way we can conceive of the origin of gastric, intestinal, sexual, heart, and respiratory neuroses. But no one has as yet thought of conceiving neuroses of internal glands under this neurochemical viewpoint. Another factor which enters into this aspect of the etiology of organ neuroses, and which might be added as number three to the two already defined, is what might be called "psychic pathbreaking," by which is meant the facility with which neurochemical influences are made to go in one definite direction to a certain organ because the individual has his or her attention concentrated upon that organ.

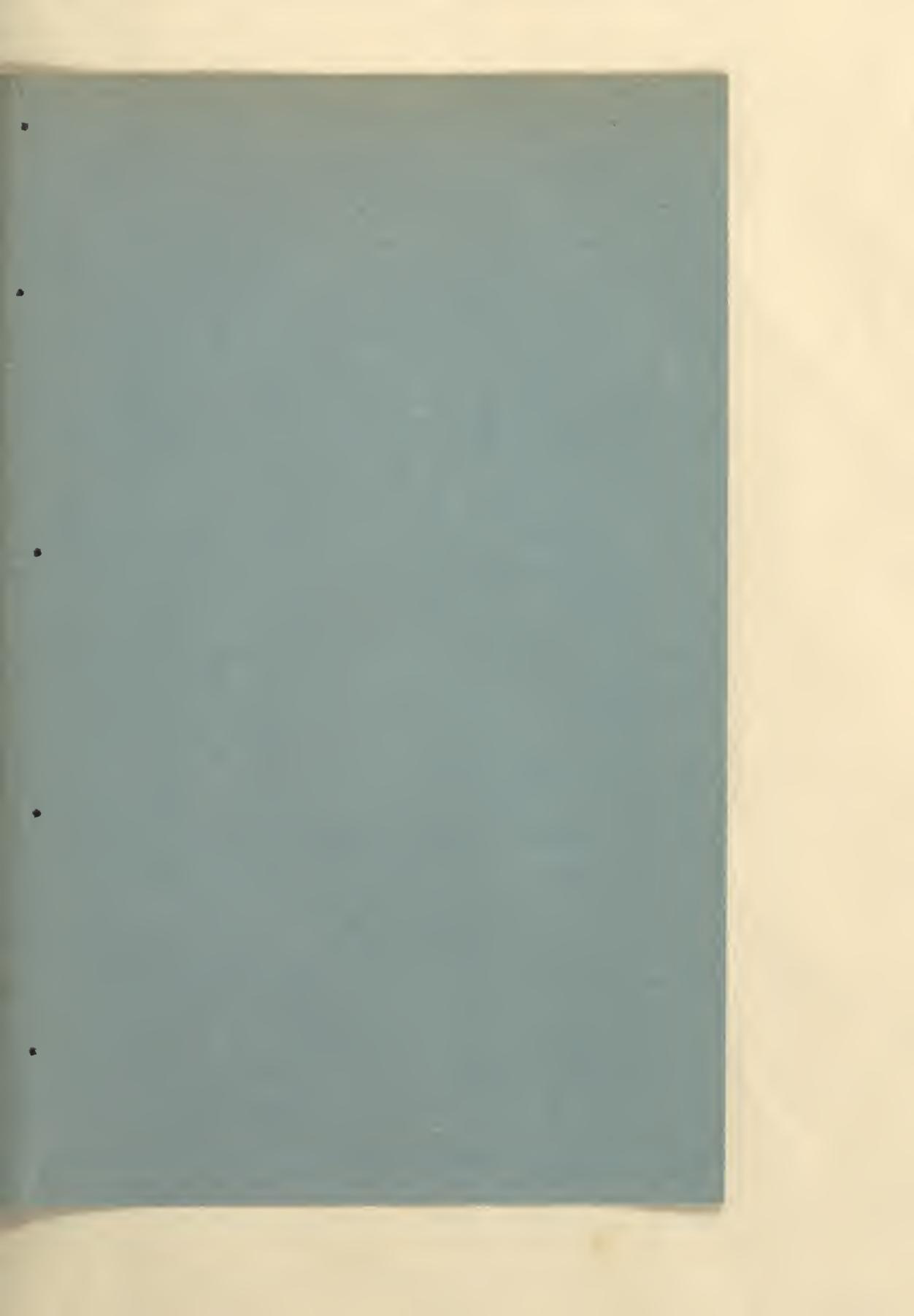
We therefore have three conditions in the development of organ neuroses: First, a heightened nerve excitability; second, increased reactive power of the organ of response; and third, psychic facilitation by the attention. It is evident in considering the dissociation of neurotropic substances that those organs which are most readily and most easily appealed to are in the foreground with their effects. Patients that are already stomach sufferers will predominately react to epinephrine and pilocarpine by gastric symptoms. Asthmatic patients will react to very small doses of pilocarpine with profuse bronchial secretion. I must also emphasize, in this connection, that the three states—increased excitability, increased reactive power of the organs, and increased psychic facilitation—may, one or all, be affected in the same or opposite direction. They may be inhibited, and therefore we may have organs of a lessened responsive power. All this goes to show the immense complexity of the problem of pharmacodynamic and physiological parallels in the autonomic and sympathetic nervous system.



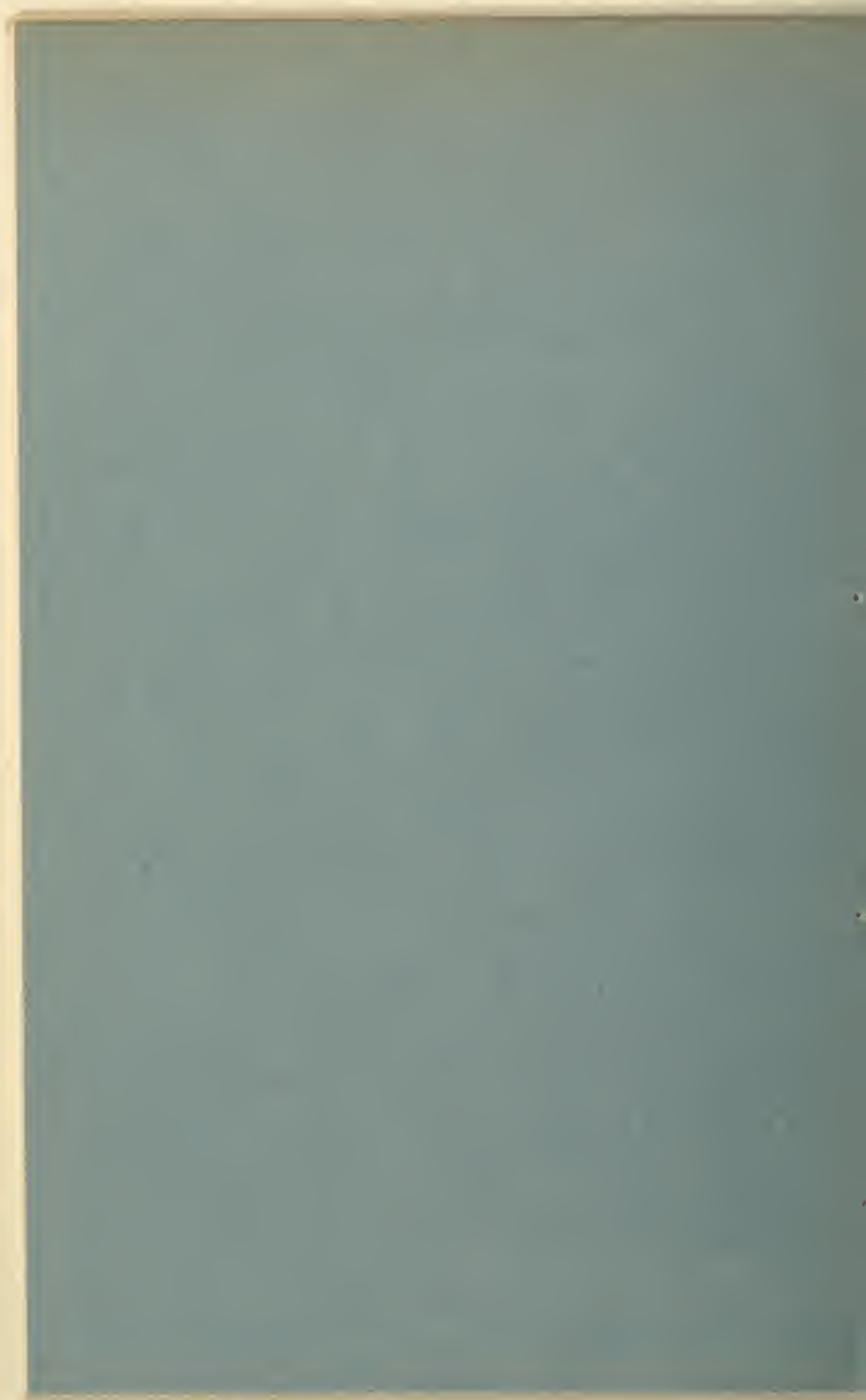












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zur chemischen Physiologie und Pathologie.

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*Sonderabdruck aus 63. Band, 2. und 3. Heft.*

John C. Hemmeter:

Vagushemmung und die anorganischen Salze  
des Herzens. I.



Berlin.

Verlag von Julius Springer.

1914.

Die

## Biochemische Zeitschrift

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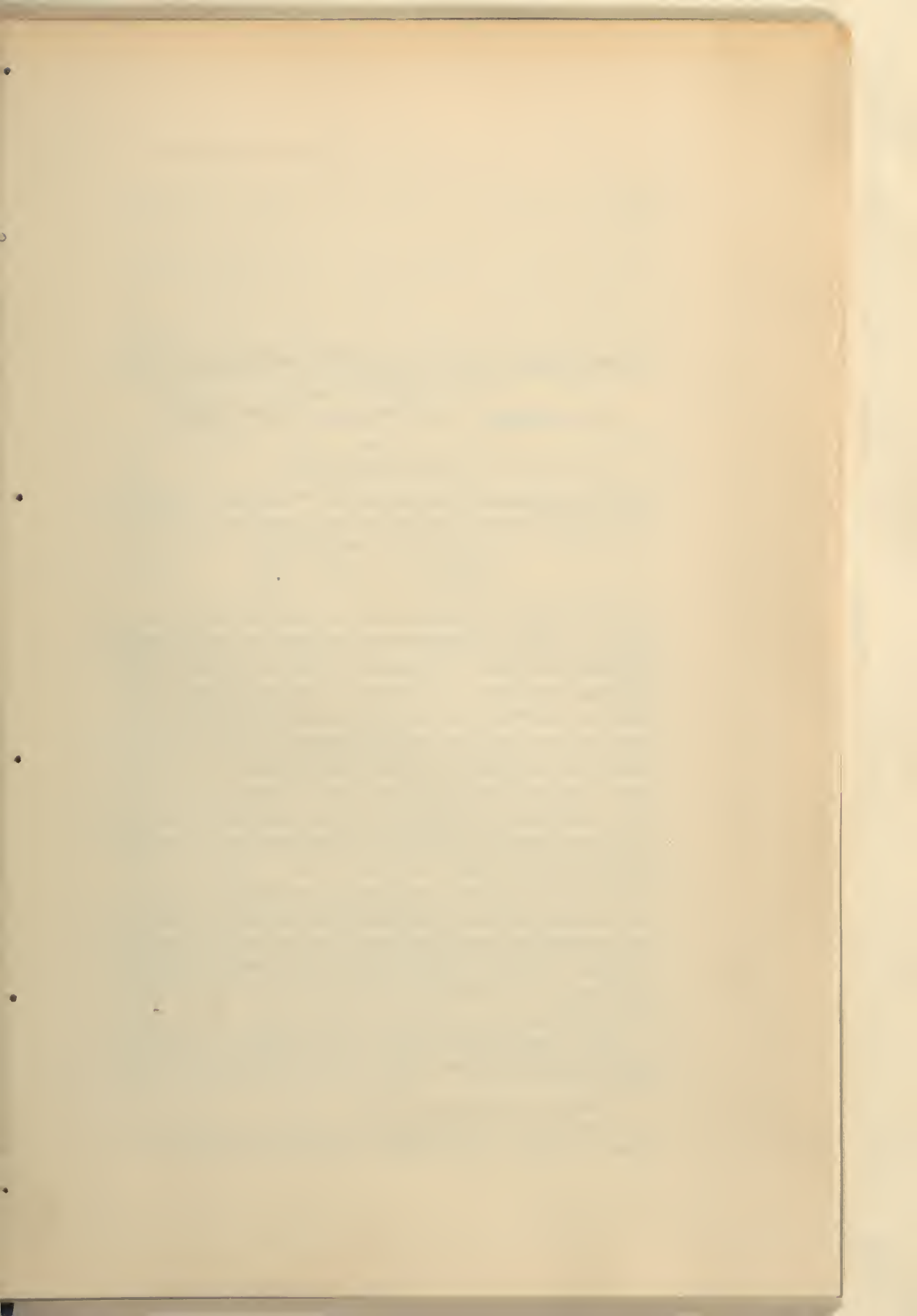
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## Vagushemmung und die anorganischen Salze des Herzens.

I. Mitteilung.

### Untersuchungen am Herzen von Elasmobranchiern.

Von

John C. Hemmeter.

(Aus dem Biochemischen Laboratorium der U. S. Bureau of Fisheries zu Wood's Hole, Mass. und dem Physiologischen Laboratorium der University of Maryland in Baltimore.)

(Eingegangen am 3. März 1914.)

Das Wesen der Vagushemmung des Herzens ist in den letzten 15 Jahren Gegenstand sehr eingehender experimenteller Forschungen gewesen. Vielleicht der erste, der in der Vagushemmung vorzüglich eine chemische Erscheinung sah und beobachtete, daß Kalium sie beförderte, war Löwit im Jahre 1882<sup>1)</sup>. Doch kann darüber kein Zweifel bestehen, daß die Bedeutung von Calcium und Kalium für die Herztätigkeit zuerst in physiologisch überzeugender Weise von Ringer dargetan worden ist. Eine vollständige Übersicht über die hier bezügliche Literatur und eine meisterhaft kritische Beleuchtung der Frage findet man bei R. Tigerstedt<sup>2)</sup>.

Die umfangreichsten und zugleich gründlichen experimentellen Untersuchungen über den Einfluß der Vagushemmung auf die anorganischen Salze des Herzens verdanken wir in Amerika Howell. Sie sind verschiedentlich im American Journal of Physiology in den Jahrgängen 1898 bis 1906 von ihm veröffentlicht worden.

Ein genaues Verzeichnis der Howellschen Arbeiten befindet sich am Ende dieser Mitteilung. In seiner letzten Unter-

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<sup>1)</sup> Arch. f. d. ges. Physiol. 25, 473.

<sup>2)</sup> Die chemischen Bedingungen für die Entstehung des Herzschlages. Ergebn. d. Physiol., 12. Jahrg., S. 269.

suchung sowie in den 1905 und 1908 im Amer. Journ. of Physiol. erschienenen, ebenso wie in seinem Lehrbuch der Physiologie, 4. Aufl., spricht E. Howell klar und eindeutig die Theorie über die chemische Natur der Vagushemmung aus, die wir hier wörtlich wiedergeben: „Die Ergebnisse der Versuche deutete ich dahin, daß der Stillstand des Herzens auf dem Vorhandensein diffusibler Kaliumverbindungen im Herzgewebe beruht, und daß die Vagusimpulse, indem sie die Menge derartiger Kaliumverbindungen vergrößern, indirekt wirken“<sup>1)</sup>.

Dieselben Versuchsreihen wurden außerdem als Beweis für die Tatsache ausgelegt, daß eine Vermehrung der Kaliumsalze in dem zirkulierenden Medium die Empfindlichkeit des Herzens in bezug auf die Vagushemmung steigert, während vollständiges Fehlen dieser Salze die Vaguskontrolle über die verschiedenen Herzkammern vermindert oder gänzlich ausschaltet.

Derselbe Forscher<sup>2)</sup> gibt als Endergebnis seiner Versuchsreihen über die durch Lockesche Lösung künstlich erhaltene Herzfunktion am isolierten Säugetierherzen an: „Vagusreizung verursachte unter diesen Bedingungen eine Vermehrung im Kaliumgehalt der umlaufenden Zirkulationslösung. Unter den obwaltenden Versuchsbedingungen, nämlich bei wiederholter Umspülung mit einer kleinen Menge der Lösung und bei maximaler Reizung des Nerv. vagus, betrug die Steigerung im Kaliumgehalt sogar 29%. Diese Steigerung beziehen wir auf ein Freiwerden von Kalium aus der Herzsubstanz, das wahrscheinlich darauf zurückzuführen ist, daß die hemmenden Nervimpulse eine Dissoziation einer indiffusiblen Form von Kaliverbindung verursachen. Nach unserer Schätzung kann jeder Reiz (eine halbe bis ganze Minute dauernd) zwischen 0,4 und 0,5 mg Kalium in Freiheit setzen. In der Voraussetzung, daß der Prozeß sich im Aurikelgewebe oder in einem bestimmten Teil der Aurikel abspielt, müßte diese Kaliummenge hinreichen, um das Herz zum Stillstand zu bringen. Die mitgeteilten Ergebnisse teilen wir folglich als Beweismaterial für die Anschauung mit, daß die hemmende Einwirkung des Vagus auf die Herzfunktion durch

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<sup>1)</sup> Amer. Journ. of Physiol. 15, 294, 1905.

<sup>2)</sup> Amer. Journ. of Physiol. 21, 63, 1908.

den Einfluß der diffusiblen Kaliumsalze vermittelt wird, die durch Hemmungsreize ausgelöst werden.“

„Reizung des Nerv. vagus erzeugt keine, wenigstens mit der uns zu Gebote stehenden Methode, nachweisbare Veränderung im Calciumgehalt der zirkulierenden Flüssigkeit.“

„Reizung des Acceleratornervs bedingt keine Erhöhung des Kaliumgehalts der Perfusionslösung.“

In seinem Lehrbuch der Physiologie (S. 570/71) schreibt Howell folgendes:

„Eine für das Herz in höherem Grade spezifische Theorie ist vom Verfasser aufgestellt worden. Es konnte in Versuchen am isolierten Hundeherzen gezeigt werden, daß während der Vagusreizung Kalium in diffusibler Form vom Herzmuskel (Aurikel) ausgeschieden wird. Es ist eine bekannte Tatsache, daß Kaliumsalze in gewisser Konzentration in der umlaufenden Flüssigkeit den Herzschlag aufheben. Die auf solche Weise verursachte Hemmung durch Kalium ähnelt sehr dem Zustande der Vagushemmung. Da der gereizte Vagus diffusibles Kalium frei macht, so sprechen wir die Vermutung aus, daß seine, die Herztätigkeit einstellende Wirkung durch Vermittlung dieser Substanz zustande kommt. Kalium in gebundener Form macht einen hohen Bruchteil der Herzmuskelsubstanz aus; diese wird nach unserer Hypothese durch die Vagusimpulse dissoziiert oder gespalten, so daß lösliches Kalium abgetrennt wird. Findet nun diese Abtrennung in demjenigen Teile des Herzens statt, in dem der Herzschlag seinen Ursprung nimmt, so liefert diese Theorie eine einfache Erklärung für den Stillstand des Herzens sowie für seine schnelle Erholung nach Unterbrechung des Reizes und für seine andauernde Irritabilität gegenüber direkter Reizung während der Vagushemmung. Ein Herz, das durch überschüssiges, dem umlaufenden Blute zugeführtes Kaliumchlorid zu schlagen aufhört, setzt sofort mit der Tätigkeit wieder ein, sobald der Überschuß an Kalium entfernt ist und erweist sich, wie bei der Vagushemmung, oft nachher kräftiger und regelmäßiger als vorher.“

Weiter sagt Howell<sup>1)</sup>: „Untersuchungen am isolierten Herzen zeigen, daß, wenn der Gehalt des zirkulierenden Mediums an Kalium 0,05 % oder sogar weniger erreicht, das Herz stehen

<sup>1)</sup> Amer. Journ. of Physiol. 21, 55, 1908.

bleibt. Unsere Versuche tun dar, daß solch eine Kaliumkonzentration im Aurikelgewebe oder in bestimmten Teilen desselben während der Vagusreizung wirklich besteht.“

Weiter heißt es (l. c. S. 63): „Nach ausgeführten Berechnungen kann jeder Reiz (von  $\frac{1}{2}$  bis 1 Minute Dauer) zwischen 0,4 bis 0,5 mg Kalium in Freiheit setzen. Angenommen, daß der Prozeß im Vorhofgewebe oder in einem gewissen Teil der Aurikel abläuft, so genügt diese Kaliummenge zur Hemmung des Herzens.“

In einer Untersuchung über den opsonischen Index spricht Sir A. E. Wright<sup>1)</sup> über zwei Arten von Fehlern, die bei wissenschaftlichen Urteilen auf Grund von Versuchen und Beobachtungen unterlaufen können. Die eine Art könnte man den mathematischen, die andere den funktionellen Fehler nennen. Der mathematische Fehler liegt in der Methode selbst begründet, so daß der Experimentator dafür nicht direkt verantwortlich gemacht werden kann. Der funktionelle wird durch mangelhafte Sinnesschärfe oder durch falsche Deutung des Untersuchers selbst bedingt. Es ist nicht meine Absicht, an der schönen Arbeit, die ich zitiert habe, Kritik zu üben. Jedoch ist es ohne weiteres einleuchtend, daß die Methode, die die chemische Wage anstatt eines colorimetrischen Vergleichs mit einer Standardlösung benutzt, zweifellos vorzuziehen ist, weil die Möglichkeit des mathematischen Fehlers dabei auf ein Minimum reduziert ist.

Ostwald behauptet in seiner Naturphilosophie, daß ein Fehler von 0,07% bei jeder Analyse zu erwarten ist, und daß es nur Meistern der chemischen Technik gelingt, Resultate zu erlangen, die innerhalb einer engeren Fehlergrenze liegen. In der Methode von Cameron und Failyers gibt es acht verschiedene Stufen im Analysengang, und bei jeder ist ein Fehler im positiven oder negativen Sinne möglich, der durch Wägung nicht kontrolliert werden kann<sup>2)</sup>.

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<sup>1)</sup> Proc. Roy. Soc. 3, 1910. Siehe auch Kritik von K. Pearson in Biometrika 8, 172, Juli 1911.

<sup>2)</sup> Die Methode der Kaliumbestimmung in den zitierten Versuchen war folgende:

Colorimetrische Methode zur Kaliumbestimmung von Cameron und Failyer (Journ. Amer. Chem. Soc. 25, 1063 und Bull. 31. U. S. Dept.



Verfasser ging von der Idee aus, daß man an das Problem der Vaguswirkung auf die Elektrolyte des Herzens mittels einer Methode herangehen könne, in der die chemische Wage verwandt wird. Unter der Voraussetzung, daß die Vagusreize in der Tat durch eine Dissoziation oder Spaltung des Kalium, das vorher mit der Muskelsubstanz chemisch gebunden war, in löslicher Form frei machen, ergibt sich die Folgerung, daß das durch möglichst lange Reizung des N. vagus wiederholt gehemmte Herz weniger Kalium enthält als ein normales Herz derselben Tierspezies, das nicht auf diese Weise gehemmt worden ist.

Es handelt sich also bei der Lösung dieser Frage in letzter Linie darum, soviel wie möglich fettfreie Substanz aus Herzen einer gewissen Tierart zu erhalten, die unterbunden und während des Stillstandes exzidiert worden sind. Weiter heißt es dann, sie auf ihren Prozentgehalt an Kalium, Natrium und Calcium zu analysieren und sie mit derselben Menge fettfreier Trockensubstanz von Tieren derselben Spezies zu vergleichen, bei denen der Vagus nicht gereizt und das Herz nicht zum Stillstand gebracht worden ist.

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of Agric. 1906), modifiziert von Howell und Duke (Amer. Journ. of Physiol. 21, 61).

Die Methode beruht auf der Bildung eines Dijodids aus Chlorkaliumplatinat und Kaliumjodid.

1. Die Methode ist im einzelnen folgende: 2 ccm der zu untersuchenden Lösung werden in einen Platintiegel gebracht und mit 1 bis 2 ccm verdünnter Schwefelsäure (1 bis 4) versetzt. Die Lösung wird auf dem Wasserbad bis zur Trockenheit eingedampft, auf dem Sandbade erhitzt, bis der Überschuß an Schwefelsäure ausgetrieben ist, und dann über einem Bunsenbrenner bei Rotglut verascht.

2. Die Asche wird mit einigen Tropfen (10) Salzsäure (1 Teil Säure, 1 Teil Wasser) und mit wenigen Tropfen (4) einer Platinchloridlösung (1,73 g auf 25 ccm Wasser) angefeuchtet. Diese Lösung wird langsam fast bis zur Trockne auf dem Wasserbad eingedampft und die Verdampfung gerade bis zur Trockenheit bei niedriger Temperatur ausgeführt.

3. Der Rückstand wird dann gründlich mit 95%igem Alkohol durch Abgießen und Zentrifugieren wie folgt ausgewaschen: 4 oder 5 ccm Alkohol werden über den im Tiegel befindlichen Rückstand gegossen, derselbe mit einem Glasstab verrührt, dann abdekantiert und in eine Zentrifugenröhre gegossen. Ein Teil des unlöslichen Rückstandes gelangt in das Röhrchen, ein anderer bleibt im Tiegel. Diese Waschung wird 5 mal

Ist die Theorie richtig, so dürfen wir mit Recht erwarten, daß die fettfreie Trockensubstanz von gehemmten Herzen weniger Kali enthält als diejenige des ungehemmten.

Diese Untersuchungen wurden in den Laboratorien der U. S. Fisch-Kommission in Woods Hole, Mass., im Juni 1911 begonnen. Die dazu benutzten Versuchstiere waren Elasmobranchier, besonders der Hundshai (*Mustelus canis* oder *Cynais canis*).

Nächsthäufig kam der Sandhai (*Carcharias littoralis*) zur Verwendung, und schließlich wurden auch Herzen der Riesenschildkröte (*Caretta caretta*) experimentell verarbeitet. Die Technik der Vagusversuche an den Elasmobranchiern ist bereits vom Verfasser veröffentlicht worden<sup>1)</sup>. Die dort beschriebene operative Technik ist sowohl beim Hundshai, Haifisch und Scyllium verwendbar, nur beim Rochen (*Raja*) muß sie entsprechend modifiziert werden.

In der zitierten Abhandlung sind die Gründe angegeben,

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wiederholt. Der Tiegel, der noch Reste des Rückstandes enthält, wird auf dem Wasserbade getrocknet.

4. Die Zentrifugenröhre wird einige Minuten lang in die Zentrifuge gebracht. Das Präcipitat ist so schwer, daß kurzes Zentrifugieren genügt, um den überstehenden Alkohol abzugießen, ohne daß der Bodensatz mitgerissen wird.

5. Letzterer wird dann mehrere Male mit einigen Kubikzentimetern Alkohol durch Zentrifugieren und Dekantieren ausgewaschen. Den so gereinigten Rückstand trocknet man auf dem Wasserbade.

6. Die Rückstände aus der Röhre und dem Tiegel werden hierauf in einer solchen Menge heißen Wassers aufgelöst, daß die Lösung 25 bis 50 ccm beträgt.

7. Nach Abkühlen entwickelt man die Färbung durch Ansäuerung mit HCl und Zusatz von 1 bis 2 ccm einer 25%igen Kaliumjodidlösung. Die Lösung färbt sich allmählich tiefrot. Es ist aber zweckmäßiger, die Lösung erst 10 bis 12 Stunden vor der colorimetrischen Bestimmung stehen zu lassen. Zu diesem Behufe wird die Lösung bis auf 100 ccm aufgefüllt, so daß die ursprüngliche Lösung in bezug auf ihren Kaligehalt 50fach verdünnt wird. Die so aus Proben der Perfusionsflüssigkeit mit und ohne Nervenreizung erhaltenen farbigen Lösungen werden miteinander und mit einer Testlösung von Kaliumplatinchlorid verglichen. Zu den colorimetrischen Bestimmungen wurde der von Schreiner konstruierte Apparat benutzt, der befriedigendere Resultate als der Dubosq'sche lieferte.

<sup>1)</sup> Zeitschr. f. biol. Technik u. Methodik 2, 221, 1911.

warum eine spezielle Versuchstechnik für diese Fische ausgearbeitet werden mußte. Der Hauptgrund war der, daß wir nirgends Angaben über ein operatives Verfahren finden konnten, bei dem der Vagus der Elasmobranchier auf zuverlässige Weise, ohne das Leben des Fisches sofort zu gefährden, für experimentelle Zwecke bloßgelegt werden kann. Die Methode der Freilegung des Herzens ist auch schon in jener Arbeit beschrieben, auf die wir zur näheren Orientierung über die Technik verweisen möchten.

Zwecks Erlangung gehemmter Herzen wurden die Selachier mit einer 10<sup>0</sup>/<sub>0</sub>igen Chloretonlösung in Seewasser narkotisiert, angebunden, die Vagi bloßgelegt und mit einem Faden gesichert. Während der ganzen Operationszeit wurden die Kiemen des Fisches soviel wie möglich unter Seewasser gehalten.

Nachdem man den Vagus losgelöst und gesichert hatte, wurde das Tier auf den Rücken gelegt und das Herz, wie in der schon erwähnten Arbeit beschrieben, bloßgelegt. Vier Ligaturen werden lose unter dem Herzen durchgeführt. Zwei davon so nahe wie möglich an dem hinteren Ende des Sinus venosus, und die zwei anderen auf der Aorta, gerade unterhalb des Bulbus arteriosus. Das Herz wird mehrere Male zum Stillstand gebracht, wobei man sich zeitlich nach dem Metronom oder der Stoppuhr richtet. Während einer Hemmung, also eines absoluten Herzblocks, werden die Fäden fest zusammengezogen, das Herz durch einen Schnitt zwischen die beiden Fäden beim Sinus-venosus-Ende und zwischen die beiden anderen Fäden kopfwärts zum Bulbus arteriosus freigemacht. Aus dem Pericardium wird es ohne Blutung herausgenommen, in einen Kolben oder eine breite Porzellanschale gelegt. Dann schneidet man die Ligaturen ab und läßt das Herz durch seine eigenen systolischen Contractionen das in ihm enthaltene Blut auspressen. Auch nach gänzlicher Blutentleerung pressen sich diese Herzen regelmäßig noch 1 bis 2 Stunden nach der Entfernung aus dem Herzbeutel zusammen. Hierauf trocknet man sie behutsam durch Rollen in aschefreiem Filtrierpapier, bringt sie abermals in Porzellanschalen und trocknet sie zur Gewichtskonstanz im Trockenschrank oder in einem Exsiccator über H<sub>2</sub>SO<sub>4</sub>.

Nach absoluter Trocknung werden die Herzen zu Pulver vermahlen, dann nochmals bis zur Gewichtskonstanz getrocknet,



um zu kontrollieren, ob sie sich während des Mahlens mit Wasser angereichert haben.

Das aus den während der Hemmung exzidierten Herzen gewonnene Blut wird auch bis zur Gewichtskonstanz getrocknet, zu Pulver zerrieben und in einem luftdicht abgeschlossenen Gefäß zur quantitativen Analyse aufbewahrt, die mit derjenigen von normalem Blut des Hundshais oder des Haifisches verglichen wird. Denn nach unserer Überlegung müßte, wenn die Herzhemmung mit der Kaliumausscheidung aus der Aurikel- oder Ventrikelsubstanz verknüpft ist oder von ihr abhängt, das in diesen Kammern befindliche Blut während des Lähmungs-zustandes mehr Kalium (einen höheren Prozentgehalt) aufweisen als das normale Blut derselben Tierart, das aus einem nicht gehemmten Herzen stammt. Das trifft natürlich nur zu, wenn große Mengen beider Blutarten analytisch verglichen werden.

Wir möchten vorweg bemerken, daß das von der U. S. Fisch-Kommission gelieferte lebende Material überaus reichlich war, so daß es uns jetzt schwer fällt, genaue Zahlen der so operierten Hunderten von Elasmobranchiern zu geben, deren Herzen auch chemisch untersucht wurden. Da jedoch Versuche an dieser Klasse von Tieren verhältnismäßig selten sind und diese Gattung Elasmobranchier die Hauptmasse von lebendigem Material in marinen Laboratorien ausmachen, erweisen wir anderen Forschern auf diesem Gebiete durch einige Angaben über das Herzgewicht, das einem gewissen Lebendgewicht von Fischen entspricht, vielleicht einen Dienst.

Das Durchschnittsgewicht von 200 mit den Fangnetzen der U. S. Fisch-Kommission zu Woods Hole, Mass., im August 1911 gefangenen Hundshaien betrug 1,98 kg. Die Fische wurden unmittelbar nach ihrem Transport in das Laboratorium gewogen. Während der Abwägung befanden sie sich in einem großen Aquarium, dessen Gewicht genau vorher bestimmt worden war. Nach der Arretierung des Herzens und seiner Exzision wurde es frisch in nassem Zustande gewogen, bis zu konstantem Gewicht im Thermostaten oder im Exsiccator über Schwefelsäure getrocknet und nochmals gewogen. Auf diese Weise wurde festgestellt, daß die Menge Wasser, oder genauer ausgedrückt, flüchtige Substanz im Herzen dieser Fische 81,2% betrug.

Durch Wägung von mehreren hundert Fischen im natür-



lichen Zustände und von ihren Herzen sogleich nach der Ausschneidung konnten wir ermitteln, daß  $0,000879\%$  des Gesamtkörpergewichts des Hundshaies das Gewicht des frisch entnommenen Herzens darstellen. Berücksichtigt man die beim Trocknen verloren gehende Wassermenge, so kann man annähernd die Trockensubstanz des Herzens eines bestimmten Fischgewichts berechnen. Nicht ganz ein Fünftel des Herzgewichts macht die Trockensubstanz aus. Nach Wägung des Fisches wurde der normale Puls registriert.

Das Herz des Haifisches (*Carcharias littoralis*) kann nicht länger als 20 Sekunden in einem Hemmungszustand gehalten werden, wenn nicht beide Vagi gleichzeitig gereizt werden. Man muß deshalb unbedingt darauf achten, wenn man das im Ventrikel während des vollständigen Stillstandes befindliche Blut erhalten will, daß der Venensinus und der Arterienbulbus von Ligaturen umgeben sind. Jedes Paar der Fäden muß von den Händen verschiedener Personen festgehalten werden, d. h. einer hält beide Enden der Sinus-venosus-Naht, der andere beide Enden der Bulbus-arteriosus-Ligatur, während ein dritter die Vagi reizt und die Hemmung hervorbringt. Hat dies während 10 bis 15 Schlägen des Metronoms, das 60 Schläge in der Minute ausführt, angedauert, so werden beide Fäden fest angezogen. Sollte unerwartet eine systolische Contraction eintreten, bevor die Fäden zusammengezogen sind, so ist es am ratsamsten, die Reizung der Vagi zu wiederholen; denn eine einzige Systole genügt natürlich, um das im Ventrikel befindliche Blut auszupressen. Wir würden dann unmöglich gerade denjenigen Teil des Blutes bekommen, den wir in bezug auf die Elektrolyte, namentlich die K-, Na- und Ca-Salze, analysieren wollen, weil sie wahrscheinlich das Myocardium schon verlassen haben werden. Das Herz der Riesenschildkröte (*Caretta*) und des Hundshais kann längere Zeit als dasjenige des Hais gehemmt werden.

Im folgenden sollen diese zwei Herzarten als (A) gehemmte und (B) normale Herzen unterschieden werden. Die chemischen Analysen wurden getrennt in zwei verschiedenen Laboratorien ausgeführt. Zuerst in dem wissenschaftlichen Laboratorium von Prof. Dr. A. Rosenheim und Prof. Dr. R. J. Meyer in Berlin. Diese Chemiker wurden mir aufs wärmste von A. Magnus-Levy

empfohlen, dessen Arbeit über den Gehalt der menschlichen Organe an Chlor, Calcium, Magnesium, Eisen sowie Wasser, Eiweiß und Fett mit zu dem Besten gehört, was überhaupt veröffentlicht worden ist<sup>1)</sup>.

Eine zweite Analysenreihe, die auch in dieser Arbeit aufgenommen ist, wurde von Herrn D. E. Worrall und dem Verfasser im Biochemischen Laboratorium der U. S. Fisch-Kommission in Woods Hole, Mass., durchgeführt. Herr D. E. Worrall hat bei mir auf Empfehlung des Direktors der chemischen Abteilung der Harvard-Universität, Prof. Baxter, gearbeitet.

Eine dritte Reihe von analytischen Untersuchungen unternahm der Chemiker Herr C. Glaser in Baltimore, jedoch nicht an demselben Material, das Worrall und den Berliner Chemikern zur Verfügung stand. Obgleich die von Hans Aron<sup>2)</sup> beschriebene Methode benutzt werden sollte, ergab sich bei einer Prüfung der Glaserschen Resultate, daß letzterer anderen Methoden den Vorzug gab. Seine Ergebnisse werden später mitgeteilt werden.

Die Untersucher glaubten die besten Resultate zu erzielen, wenn sie nach den ihnen am meisten vertrauten Methoden und nicht alle nach ein und derselben arbeiteten, wie es eigentlich im Versuchsplan als notwendig angeordnet worden war. Dies verursachte sehr viel Extraarbeit, namentlich da Duplikatproben von getrockneter Herzsubstanz nach Berlin geschickt werden mußten.

In der vorliegenden Abhandlung werden nur die Analysen der Trockensubstanz von Herz und Blut des Hundshais (*Mustelus canis*) und des Hundeherzens erörtert werden. Bei beiden Tierespezies wird die Bestimmung des normalen Herzens mit dem im Zustande der Hemmung verglichen, ebenso die des normalen Blutes mit demjenigen, das aus dem Ventrikel während des Herzstillstandes stammt.

Außer am Hundshai wurden normale und in ihrer Funktion gehemmte Herzen der Schildkröte (*Caretta*) von C. Glaser in Baltimore analytisch verarbeitet, ebenso von Haifischen (*Carcharia littoralis*) von Professor Rosenheim und Meyer in Berlin. Es wäre wünschenswert gewesen, daß an beiden Arbeitsstätten Parallelanalysen des Schildkröten- wie des Haifischherzens ausgeführt worden wären. Das war leider unmöglich

<sup>1)</sup> Diese Zeitschr. 24, 363, 1910.

<sup>2)</sup> Handb. d. biochem. Arbeitsmethoden 1, 404.

aus Mangel an Material, denn während des ganzen Sommers 1911 konnten nicht genügend Haifische oder Schildkröten gefangen und dem Laboratorium geliefert werden, um die drei genannten Laboratorien mit Herztrockensubstanz hinreichend zu versorgen.

### Methode der quantitativen Bestimmung.

Alle genannten Chemiker verfahren nach der von H. Aron<sup>1)</sup> beschriebenen Methode.

Man muß eine bestimmte chemische Methode vollkommen beherrschen, wenn es sich auch nur darum handelt, die Resultate zweier verschiedener Untersucher zu beurteilen und zu vergleichen, und nicht zur Verwertung der eigenen Ergebnisse. Das wird am besten dadurch erreicht, indem man die Methode an einer Substanz wiederholt ausführt, die einen bekannten Gehalt desjenigen Salzes aufweist, das quantitativ ermittelt werden soll. Abderhalden empfiehlt zu diesem Zweck eine Mischung verschiedener Salze mit aschefreiem Zucker, der nachher verascht wird. Fortgesetzte Untersuchungen und Übungen werden nun an dieser Mischung vorgenommen, die besonders lehrreich sind, wenn die Salze zueinander prozentisch in solch einem Verhältnis stehen, wie es beim wirklichen Untersuchungsmaterial der Fall ist.

Bevor ich nach Woods Hole ging, machte ich mich mit der oben angegebenen Methode in Abderhaldens Handbuch der biochemischen Arbeitsmethoden vollständig vertraut. Im chemischen Laboratorium der Universität von Maryland führte E. P. Doetsch mit mir eine Anzahl Bestimmungen von Kalium, Natrium, Calcium und Magnesium in der Asche der Herzen einer kleinen Schildkröte, *Pseudemus rugosa*, aus, wie auch in derjenigen von Schweineherzen. Von diesen Analysen ist keine hier veröffentlicht. Sie werden mitgeteilt werden, sobald unsere Analysen aller Säugetierherzen fertig vorliegen.

Was die Genauigkeit der erhaltenen Resultate betrifft, so ist zur logischen Deutung der Analysenzahlen nach all den mühsamen Manipulationen des Veraschens, Fällens, Waschens, Filtrierens, Wägens etwas Erfahrung im chemischen Denken notwendig. Magnus-Levy<sup>2)</sup> und auch Hans Aron geben wertvolle Vorsichtsmaßregeln für die Beurteilung der Zahlen,

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<sup>1)</sup> l. c.

<sup>2)</sup> l. c. S. 366.



namentlich in bezug auf die zulässige Breite des funktionellen und mathematischen Fehlers. Magnus-Levy sagt, daß eine Differenz von 0,6 mg Ca in 30 g frischer Substanz (das wären 2 mg für 100 g) eine erlaubte Abweichung wäre<sup>1)</sup>.

### Kritische Erörterung über die Frage der Vagushemmung und der anorganischen Salze des Herzens.

Die sorgfältigen Analysen von Prof. R. Meyer sowohl wie von Herrn D. E. Worrall zeigen durchgehends, daß die Trockensubstanz des Herzens von Fischen (*Mustelus canis*) wie auch desjenigen von Säugern (Hund), das im Zustande kompletten Stillstands ausgeschnitten worden ist, gegenüber dem un-gehemmten Herzen (also dem von uns als normal bezeichneten) mehr Kaliumsalz enthält. Mithin muß also Kalium eine gewisse Rolle bei der Vagushemmung spielen.

Doch weisen die Versuche darauf hin, daß dieses Kalium nicht aus dem Herzen stammt, sondern vielmehr erst dort eingedrungen zu sein scheint. Damit kommen wir in unserem Gedankengange nun weiter zu der Vermutung, daß das, was im Blute enthalten ist, nicht auch Bestandteil der Muskelsubstanz sein muß. Also, müssen wir konsequenterweise folgern, wird die Herzhemmung nicht durch Austritt des Kaliums aus dem Herzen und Übertritt ins Blut verursacht, sondern umgekehrt, durch Austritt aus dem Blut und Übertritt in das Herz. Dieser Schluß darf jedoch nicht auf Grund von 2 bis 3 Analysen, die jeder Chemiker ausgeführt hat, gemacht werden. Die klassische, bahnbrechende Arbeit Howells hat uns den Weg zur Erforschung des Vagusproblems vom rein biochemischen Standpunkte aus gewiesen und die Erscheinung der Herzhemmung eindeutig mit der Gegenwart von Kaliumsalzen verknüpft. Die im vorstehenden mitgeteilten Versuche beweisen nur, daß es mit Hilfe der benutzten chemischen Methoden nicht möglich ist, die Behauptung zu bestätigen, daß die Kaliumsalze aus der Herzsubstanz während der auf Vagusreizung erfolgenden Hemmung ausgeschieden werden.

Die obige Bemerkung, daß das im Blute kreisende KCl

<sup>1)</sup> Diese Zeitschr. 24, 367: „Welcher Analytiker verbürgt sich für die Richtigkeit des Gewichtes der abgeschiedenen Stoffe bis auf das Milligramm?“ (Rammelsberg!)



nicht in der Herzsubstanz selbst enthalten ist, entspricht unserer Anschauung der Kaliumwirkung auf die Muskelfaser. Nach unserer Auffassung beruht sie auf einer chemischen Verbindung des Kaliums mit dem Protoplasma der Muskelfaser. Aus diesem Grunde kann ein physiologischer Effekt nicht eher zustande kommen, als bis das Kalium sich wirklich mit einem Agens in der Muskelfaser verbunden hat. Eine andere Art der Wirkung anorganischer Salze auf Muskelfaser ist zuerst von Jacques Loeb als „Kontaktirritabilität“ beschrieben worden, aber auch in diesem Falle deutet der Autor die Wirkung als auf der Bildung von unlöslichen Calciumverbindungen beruhend. Ich persönlich glaube zwar, daß die Erscheinung auf teilweise veränderte Oberflächenspannung zurückzuführen ist. Loeb's und meine Erklärung weichen insofern voneinander ab, als ersterer annimmt, daß die Kontaktirritabilität verursachenden Stoffe mit etwas in der Muskelfaser eine Verbindung eingehen, während meiner Auffassung nach sie einfach die Oberflächenspannung des Muskels, nicht aber seine chemische Zusammensetzung modifizieren. Die Bedeutung dieser Versuche hat für unser Problem nur theoretisches Interesse. Irgendeine Substanz, die in den Herzmuskel eindringt, kann durch Vergleich quantitativer Analysen von Herzen, die sich im ungehemmten Zustande befinden, mit denen, die durch Reizung des N. vagus gelähmt worden sind, bestimmt werden.

In den Analysen der Trockensubstanz von zwei solchen Herzkategorien dürfte man wohl mit Recht quantitative Unterschiede in den uns interessierenden anorganischen Salzen (KCl, NaCl,  $\text{CaCl}_2$ ) erwarten. Wenn aber das eine oder das andere dieser Salze eine Wirkung entfaltet, indem es einfach die Oberflächenspannung der einzelnen Muskelfibrille ändert, ohne sich chemisch mit einem Bestandteil derselben zu binden, so würden solche Bestimmungen von gehemmten und ungehemmten Herzen keine Unterschiede aufweisen können, wenigstens keine gesetzmäßigen oder regelmäßigen.

Mit den angewandten analytischen Methoden war es unmöglich, irgendwelche regelmäßigen Abweichungen in den Mengen anorganischer Salze in gehemmten und ungehemmten Herzen nachzuweisen. Auch ist es nicht gelungen, mit Hilfe dieser selben chemischen Methoden konstante und reguläre Mengen-

unterschiede in diesen Salzen aufzufinden, die im Blute aus den Ventrikeln gehemmter und normaler Herzen bestimmt wurden. Wir hatten angenommen, daß, wenn der Herzstillstand unter dem Einfluß der Vagushemmung auf einem Freiwerden von Kalium aus einer leicht spaltbaren Kaliumverbindung mit einem Bestandteil des Herzmuskels beruht, so dieses freigewordene Kalium im Blut, das im Ventrikel während der Hemmung enthalten ist, als Plus nachgewiesen werden müßte. Durch unsere diesbezüglichen Analysen der Herzen und des Blutes vom Hundshai konnte diese Annahme keine Bestätigung finden.

Indem wir unsere Aufgabe in diesem Stadium abbrechen, möchten wir noch auf eine demnächst erscheinende Veröffentlichung hinweisen über Untersuchungen an Herzen der Riesenschildkröte (*Caretta*) und des Hundes, die zum Zweck eines weiteren Studiums der Vagushemmung ausgeführt worden sind. Außerdem auf die hier folgende Arbeit über eine biologische Methode, mit deren Hilfe man dieses Problem in Angriff nehmen kann. Diese gestaltet sich derart, daß man nämlich erstens das aus dem gehemmten Herzen kommende Blut durch das Herz eines anderen Tieres derselben Spezies schickt, das nicht durch Vagusreizung zum Stillstand gebracht wird. In der zweiten Untersuchungsmethode handelt es sich dann darum, festzustellen, ob das Blut des gehemmten Herzens, nachdem es seine Tätigkeit wieder aufgenommen hat, bei Einpumpung in das zweite Herz imstande ist, den Herzschlag des letzteren zu verlangsamen oder aufzuheben. Wenn eine Verzögerung eintritt, so würde dies besagen, daß eine chemische Substanz das gehemmte Herz Nr. 1 verläßt, die eine Hemmung des Herzens Nr. 2 zu verursachen vermag.

#### Nachtrag.

Erklärung der Gewichtsverluste beim Trocknen. Von Prof. R. Meyer. 16. Dez. 1911.

Das Verhältnis der Vagushemmung zu den anorganischen Salzen des Herzens.

Berlin, 16. Dezember 1911.

Auf Anraten von Magnus-Levy wurden diese Analysen in dem Wissenschaftl.-Chemischen Laboratorium zu Berlin von Prof. Dr. A. Rosenheim und Prof. Dr. R. J. Meyer ausgeführt.

A.	Herz von	Carcharias	littoralis	normal.
B.	"	"	"	Vagusreizung
C.	"	"	Mustelus canis	normal.
D.	"	"	"	Vagusreizung.
E.	Blut	"	"	normal.
F.	"	"	"	Vagusreizung.

Die Wägegläschen wogen mit der Substanz;

Tag	A.	B.	C.	D.	E.
1.	21,7241	19,6212	20,6878	21,1266	24,6524
2.	21,6799	19,6000	20,6453	21,1068	24,5990
4.	21,6081	19,5712	20,5907	21,0794	24,5274
5.	21,5829	19,5658	20,5773	21,0690	24,4970
6.	21,5539	19,5576	20,5642	21,0558	24,4630
7.	21,5311	19,5466	20,5483	21,0449	24,4387
8.	21,5112	19,5400	20,5400	21,0400	24,4180
10.	21,4942	19,5328	20,5300	21,0312	24,3964
11.	21,4725	19,5225	20,5200	21,0211	24,3730
12.	21,4535	19,5154	20,6101	21,0124	24,3542
Verlust	0,2706	0,1058	0,1777	0,1142	0,2982

Das Gewicht der leeren Wägegläschen betrug:

A.	B.	C.	D.	E.
16,3078	14,1870	15,2426	15,6543	19,1878

Das Gewicht der Wägegläschen mit der Substanz minus demjenigen der leeren Wägegläschen ergibt das Gewicht der Substanz. (Die Gewichte sind am 4. Tage bestimmt, siehe oben.)

Gewicht am 4. Tage	21,6081	19,5712	20,5907	21,0794	24,5274
" des Glases	16,3078	14,1870	15,2426	15,6543	19,1878
Gewicht der Substanz	5,3003	5,3842	5,3481	5,4251	5,3396

Dezember 1911.

#### Ergebnisse der Analysen.

##### A. Herz von Carcharias littoralis.

Normal.

Menge der angewandten Substanz: 5,3003 g.

Gefunden

Berechnet auf 5 g  
Substanz

	g		g		%
CaO	= 0,0050	CaO	= 0,00472	CaO	= 0,09
Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0260	MgO	= 0,00887	MgO	= 0,18
KCl + NaCl	= 0,3990	KCl	= 0,01539	KCl	= 3,08
KClO <sub>4</sub>	= 0,3035	NaCl	= 0,22240	K <sub>2</sub> O	= 1,95
				NaCl	= 4,45
				Na <sub>2</sub> O	= 2,36
				KCl + NaCl	= 7,53

##### B. Haifischherzen (Carcharias littoralis).

Vagus gereizt. Ausgeschnitten im Hemmungszustand.

Menge der angewandten Substanz: 5,3842 g.

Gefunden		Berechnet auf 5 g Substanz		
	g		g	%
CaO	= 0,0067	CaO	= 0,00622	CaO = 0,12
Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0267	MgO	= 0,00899	MgO = 0,18
KCl + NaCl	= 0,3740	KCl	= 0,01437	KCl = 2,87
KClO <sub>4</sub>	= 0,2875	NaCl	= 0,20360	K <sub>2</sub> O = 1,82
NaCl	= 0,2159			NaCl = 4,07
KCl	= 0,1581			Na <sub>2</sub> O = 2,16

C. Herz des Hundshaies (*Mustelus canis*).

Normal. Vagus ungereizt.

Menge der angewandten Substanz: 5,3481 g.

Gefunden		Berechnet auf 5 g Substanz		
	g		g	%
CaO	= 0,0035	CaO	= 0,00327	CaO = 0,06
Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0232	MgO	= 0,00785	MgO = 0,16
KCl + NaCl	= 0,3325	KCl	= 0,14590	KCl = 2,92
KClO <sub>4</sub>	= 0,2905	NaCl	= 0,21140	K <sub>2</sub> O = 1,84
KCl	= 0,1564			NaCl = 4,22
NaCl	= 0,2261			Na <sub>2</sub> O = 2,24

D. Herz des Hundshaies (*Mustelus canis*).

Vagus gereizt.

Menge der angewandten Substanz: 5,4251 g.

Gefunden		Berechnet auf 5 g Substanz		
	g		g	%
CaO	= 0,0037	CaO	= 0,00341	CaO = 0,07
Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0280	MgO	= 0,00935	MgO = 0,19
KCl + NaCl	= 0,3613	KCl	= 0,15220	KCl = 3,04
KClO <sub>4</sub>	= 0,3067	NaCl	= 0,18080	NaCl = 3,62
KCl	= 0,1651			K <sub>2</sub> O = 1,92
NaCl	= 0,1962			Na <sub>2</sub> O = 1,92

## Blutanalysen.

Hundshaiblut — gehemmt.

F. Hundshaiblut, aus dem Innern von gehemmten Herzen unmittelbar nach Unterbindung der abdominalen Aorta und des Sinus venosus entnommen. Bezeichnet als gehemmtes Blut.

Menge der angewandten Trockensubstanz: 5,3389 g.

Gefunden		Berechnet auf 5 g Substanz		
	g		g	%
CaO	= 0,0100	CaO	= 0,00936	CaO = 0,18
Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0330	MgO	= 0,01102	MgO = 0,22
KCl + NaCl	= 0,5696	KCl + NaCl	= 0,53340	KCl + NaCl = 10,66
KClO <sub>4</sub>	= 0,2200	KClO <sub>4</sub>	—	K <sub>2</sub> O = 1,42
KCl	= 0,1163	KCl	= 0,10890	KCl = 2,18
NaCl	= 0,4533	NaCl	= 0,42440	NaCl = 8,48



## E. Blut vom Hundshai.

Normal.

Mengen von CaO, MgO, KCl, NaCl, KClO<sub>4</sub>.

Angewandte Substanz: 5,3396 g.

Gefunden		Berechnet auf 5 g Substanz		
	g		g	%
CaO	= 0,0098	CaO	= 0,00918	CaO = 0,19
Mg <sub>2</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0325	MgO	= 0,01103	MgO = 0,22
KCl + NaCl	= 0,5670	KCl	= 0,10790	KCl = 2,16
KClO <sub>4</sub>	= 0,2140	NaCl	= 0,42310	K <sub>2</sub> O = 1,37
KCl	= 0,1152			NaCl = 8,46
NaCl	= 0,4518			Na <sub>2</sub> O = 4,49

A. steht für Hai Vagus ungereizt.

B. " " " " gereizt.

C. " " Hundshai Vagus ungereizt.

D. " " " " gereizt.

E. " " " Blut normal.

F. " " " " aus gehemmtem Herz entnommen.

## Zusammenfassung.

Gefunden in 5 g fettfreier Trockensubstanz					Prozentische Werte			
	CaO	MgO	KCl	NaCl	CaO	MgO	KCl	NaCl
					%	%	%	%
A.	0,0047	0,0089	0,1539	0,2224	0,09	0,18	3,08	4,45
B.	0,0062	0,0090	0,1437	0,2036	0,12	0,18	2,87	4,07
C.	0,0033	0,0079	0,1459	0,1211	0,06	0,16	2,92	4,22
D.	0,0034	0,0094	0,1522	0,1808	0,07	0,19	3,04	3,62
E.	0,0092	0,0110	0,1079	0,4231	0,19	0,22	2,16	8,46
F.	0,0093	0,0110	0,1089	0,4244	0,18	0,22	2,18	8,48

Berechnete Resultate aus den Analysen von J. C. Hemmeter und D. E. Worrall, ausgeführt im Chem. Laboratorium der U. S. Fisch-Kommission in Woods Hole, Mass. August 1911.

Herz vom Hundshai (*Mustelus canis*).

Vagus ungereizt. Normal.

Menge der angewandten Trockensubstanz: 5,3560 g.

Gefunden		Berechnet auf 5 g Trockensubstanz		
	g		g	%
CaO	= 0,0036	CaO	= 0,0033	CaO = 0,07
MgO	= 0,0088	MgO	= 0,0082	MgO = 0,16
KCl + NaCl	= 0,3935	KCl + NaCl	= 0,3673	KCl + NaCl = 7,34
KCl	= 0,1573	KCl	= 0,1468	KCl = 2,93
NaCl	= 0,2362	NaCl	= 0,2205	NaCl = 4,41

Herz vom Hundshai (*Mustelus Canis*).

Vagus gereizt.

Menge der angewandten Trockensubstanz: 5,402 g.

Gefunden		Berechnet auf 5 g Trockensubstanz			
	g		g		%
CaO	= 0,0036	CaO	= 0,0033	CaO	= 0,07
MgO	= 0,0092	MgO	= 0,0085	MgO	= 0,17
KCl + NaCl	= 0,3633	KCl + NaCl	= 0,3362	KCl + NaCl	= 6,66
KCl	= 0,1661	KCl	= 0,1537	KCl	= 3,01
NaCl	= 0,1972	NaCl	= 0,1825	NaCl	= 3,65

## Zusammenstellung.

a) *Mustelus canis* (Hundshai).

Normal	Gereizt
KCl = 2,92 %	KCl = 3,21 %

## b) Herzsubstanz (Hund).

	Normal		Gereizt	
	I. %	II. %	I. %	II. %
CaO	= 0,05	0,06	0,03	0,03
MgO	= 0,16	0,15	0,16	0,16
KCl	= 2,35	2,34	2,87	2,75
NaCl	= 1,50	1,27	2,72	3,11
(KCl + NaCl)	= 3,85	3,61	5,59	5,86

## c) Blut aus Hundeherz.

	Normal %	Gereizt %
CaO	= 0,02	0,03
MgO	= 0,10	0,06
KCl	= 1,74	0,34
NaCl	= 2,29	3,62
(KCl + NaCl)	= 4,03	3,96

## A.

3. Hundeherz, ungereizt. 2 Analysen *a* und *b*.

Angewandte entfettete Trockensubstanz  $\left\{ \begin{array}{l} a = 14,3245 \text{ g} \\ b = 8,6644 \text{ g} \end{array} \right.$

<i>a</i> = 14,3245 g		<i>b</i> = 8,6644 g	
CaO	= 0,0044	CaO	= 0,0048
MgP <sub>2</sub> O <sub>7</sub>	= 0,0629	MgP <sub>2</sub> O <sub>7</sub>	= 0,0362
MgO	= 0,0228	MgO	= 0,0131
KCl + NaCl	= 0,5519	KCl + NaCl	= 0,3126
K <sub>2</sub> PtCl <sub>6</sub>	= 1,0991	K <sub>2</sub> PtCl <sub>6</sub>	= 0,6616
K <sub>2</sub> O	= 0,2130	K <sub>2</sub> O	= 0,1282
KCl	= 0,3370	KCl	= 0,2028
NaCl	= 0,2149	NaCl	= 0,1098

## Prozentwerte.

<i>a</i>	%	<i>b</i>	%
CaO	= 0,052	CaO	= 0,055
MgO	= 0,160	MgO	= 0,151
KCl	= 2,350	KCl	= 2,340
NaCl	= 1,500	NaCl	= 1,270
(KCl + NaCl)	= 3,850	(KCl + NaCl)	= 3,610

## B.

4. Hundeherz, gereizt. 2 Analysen *a* und *b*.

Angewandte entfettete Trockensubstanz  $\left\{ \begin{array}{l} a = 10,8122 \text{ g} \\ b = 7,0870 \text{ g} \end{array} \right.$

	<i>a</i>	<i>b</i>
	<i>g</i>	<i>g</i>
CaO	= 0,0037	= 0,0020
Mg <sub>2</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0491	= 0,0320
MgO	= 0,0178	= 0,0116
KCl + NaCl	= 0,6092	= 0,4156
K <sub>2</sub> PtCl <sub>6</sub>	= 1,0109	= 0,6360
K <sub>2</sub> O	= 0,1959	= 0,1233
KCl	= 0,3099	= 0,1951
NaCl	= 0,2933	= 0,2205

	<i>a</i>	Prozentwerte.	<i>b</i>
		%	%
CaO	= 0,034		= 0,030
MgO	= 0,160		= 0,160
KCl	= 2,870		= 2,750
NaCl	= 2,720		= 3,110
(KCl + NaCl)	= 5,590		= 5,860

## C.

## 5. Blut (Hund), ungereizt.

Angewandte Trockensubstanz = 5,8800 g.

	<i>g</i>	Prozentwerte
CaO	= 0,0011	= 0,02
Mg <sub>2</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0162	
MgO	= 0,0059	= 0,10
KCl + NaCl	= 0,2368	
K <sub>2</sub> PtCl <sub>6</sub>	= 0,3328	
K <sub>2</sub> O	= 0,0645	
KCl	= 0,1021	= 1,74
NaCl	= 0,1347	= 2,29
		KCl + NaCl = 4,03

## D.

## 6. Blut (Hund), gereizt.

Angewandte Trockensubstanz = 5,6360 g.

	<i>g</i>	Prozentwerte
CaO	= 0,0014	= 0,025
Mg <sub>2</sub> P <sub>2</sub> O <sub>7</sub>	= 0,0084	
MgO	= 0,0030	= 0,055
KCl + NaCl	= 0,2229	
K <sub>2</sub> PtCl <sub>6</sub>	= 0,0620	
K <sub>2</sub> O	= 0,0120	
KCl	= 0,0190	= 0,340
NaCl	= 0,2039	= 3,620
		KCl + NaCl = 3,960

Blut aus gereiztem Hundeherzen verliert an K, es steigt aber sein Na-Gehalt.

Aus den Tabellen von Prof. R. Meyer, die Angaben über die Gewichtsverluste der Trockensubstanz des Herzens vom Hundshai in 12 Tagen enthalten, ist ersichtlich, daß das Herz des Hundshaies wie auch des Haies, die als vollständig trocken übersandt worden waren, eben diese 12 Tage lang an Gewicht verloren. Dies beruhte jedoch nicht auf Wasserverlust, sondern auf bakteriellem Zerfall, denn es stellte sich heraus, daß die Trockensubstanz des Herzens Trimethylamin ausschied. Da es unmöglich war, ein konstantes Gewicht beim Trocknen zu erzielen, so befolgten wir den eingeholten Rat von Prof. Magnus-Levy und begannen sofort mit den Analysen trotz der mangelhaften Gewichtskonstanz. Ich möchte hier noch erwähnen, daß später, als das getrocknete Herzgewebe in Toluol oder Chloroform aufbewahrt wurde, der fortschreitende Gewichtsverlust aufhörte. Wir und Meyer machten dann Bestimmungen an Gewebe, das frei von allem Geruch, außer natürlich dem der Antiseptica, war.

Die Ergebnisse dieser letzteren Analysen unterschieden sich kaum von den ersten, nur in einigen Fällen wurden Abweichungen konstatiert, die in die Fehlergrenze fallen. Allen Bestimmungen von Prof. R. Meyer liegen die Gewichte am 4. Tage zugrunde, da er sich überzeugt hatte, daß die Substanz nach dem 4. Tage wirklich kein Wasser mehr enthielt. Wären die Bestimmungen auf Grund der Gewichte der Herztrockensubstanz am 12. Tage gemacht worden, so wären die Resultate um die folgenden Prozentwerte größer:

A.	B.	C.	D.	E.	F.
2,9 <sup>0</sup> / <sub>0</sub>	1,04 <sup>0</sup> / <sub>0</sub>	1,51 <sup>0</sup> / <sub>0</sub>	1,24 <sup>0</sup> / <sub>0</sub>	3,24 <sup>0</sup> / <sub>0</sub>	0 <sup>0</sup> / <sub>0</sub>

Diese im ungünstigsten Falle sich ergebenden Differenzen fallen durchgehends in den Bereich des analytischen Fehlers, d. h. die berechneten Prozentwerte würden eine Änderung von nur  $\frac{1}{100}$ <sup>0</sup>/<sub>0</sub> erfahren.

Prof. Magnus-Levy und Prof. R. J. Meyer sind der Meinung, daß die analytischen Ergebnisse hinreichend genau sind, und daß die Mangelhaftigkeit in bezug auf die Gewichtskonstanz der Herztrockensubstanz ohne wesentliche Bedeutung ist.

Ich möchte nicht unerwähnt lassen, daß die Resultate von D. E. Worrall, die unter meiner Beihilfe im Laboratorium des U. S. Bureau of Fishery in Woods Hole und von C. Glaser



in Baltimore an absolut frischer Herztrockensubstanz gewonnen wurden, mit denen von Prof. R. J. Meyer befriedigend übereinstimmen, was für die Richtigkeit der Anschauung der Berliner Chemiker über die Schwierigkeit der zu erlangenden Gewichtskonstanz zeugt.

Schwankungen des Gehalts an Mineralstoffen Ca, Na, K und Mg im Herzen normaler Tiere derselben Spezies.

Bei den Selachiern derselben Spezies kommen bedeutende Schwankungen im Gehalt der Ca-, Mg-, Na und K-Salze in der fettfreien Trockensubstanz des Herzens nicht vor. Da das Herz von *Scyllium* oder *Mustelus canis* 81,2% Wasser enthält und 0,000879% des gesamten Körpergewichts erst annähernd das Gewicht des normalen Herzens darstellt, kann man einzelne Herzen zwecks eines Vergleichs in den Analysen nicht verwenden. Denn so große Scyllien oder Musteli gibt es gar nicht, daß man die Analysen des Herzens eines Fisches mit dem eines anderen vergleichen könnte. Als wir die Analysendaten der Herzen zweier großer Haifische kollationierten, fanden wir die Unterschiede sehr gering innerhalb der Fehlergrenzen. Auch stehen die Zahlen von Meyer und Rosenheim in Berlin, Glaser in Baltimore und Worrall und mir aus dem Laboratorium in Woods Hole in so gutem Einklang, daß man annehmen kann, die betreffenden Salze sind in gleichen Prozentsätzen in den Herzen dieser Fische enthalten.

In den Säugetierherzen konnten wir keine bedeutenden Schwankungen im Gehalt der Elektrolyten nachweisen. So viel ergibt sich aus den Zahlen der Bestimmungen, die Prof. R. Meyer an Hundeherzen in Berlin (Dezember 1912) ausgeführt hat (siehe Tabelle).

Allerdings darf man nicht das Herz irgendeines beliebigen Hundes mit dem eines anderen in Parallele stellen, so nicht z. B. das Herz eines Jagdhundes mit dem eines fetten Mopses. Da kann es natürlich Unterschiede geben, die die Arbeit und Kosten der Analysen vergeblich machen. Immer sollte man darauf bedacht sein, Herzen von Hunden derselben Rasse und womöglich desselben Alters zu vergleichen. Ehe zur Untersuchung geschritten wird, sollten die Tiere auch ca. 4 Wochen auf gleiche Weise ernährt werden.

## Zusammenfassung.

Die Analytiker Prof. Meyer in Berlin, Glaser in Baltimore und Hemmeter und Worrall in Woods Hole, Mass., stimmen alle dahin überein, daß in einem gereizten oder vagusgehemmten Herzen des Hundshaies der CaO-Gehalt so gut wie unverändert bleibt, daß die Menge von MgO etwas erhöht und diejenige von NaCl deutlich verringert ist.

Alle drei Bestimmungen von R. J. Meyer und zwei von Hemmeter und Worrall harmonieren auch in bezug auf das KCl. Nach Meinung dieser Untersucher verliert das gereizte und gehemmte Herz nicht an KCl, sondern sein Gehalt an KCl wird dadurch minimal gesteigert. Nach Hemmeter und Worrall steigt die KCl-Menge um 0,08%, nach R. J. Meyer um 0,12% bei Vagusreizung und Vagushemmung.

Die sehr geringen Abweichungen im KCl-Prozentgehalt des gehemmten und normalen Herzens in den Analysen von C. Glaser in Baltimore überschreiten nicht die Fehlergrenzen.

Schlußfolgerungen aus den an Hundshaiherzen ausgeführten Analysen von J. C. Hemmeter und D. E. Worrall, Woods Hole, Mass., August und September 1911.

Bei Vagusreizung erleiden die anorganischen Salze des Herzens, berechnet auf 5 g fettfreie Herztrockensubstanz, folgende Veränderungen:

CaO . . .	keine Veränderung	
MgO . . .	steigt um 0,0003	MgO = 0,01%
KCl . . .	" " 0,0069	KCl = 0,13%
NaCl . . .	fällt " 0,0296	NaCl = 0,59%

Schlußfolgerungen aus den an Hundshaiherzen ausgeführten Bestimmungen von Prof. R. J. Meyer, Berlin, Dezember 1911.

Bei Vagusreizung erleiden die anorganischen Salze des Herzens, berechnet auf 5 g fettfreie Herztrockensubstanz, folgende Veränderungen:

CaO . . .	praktisch keine Veränderung	
MgO . . .	steigt um 0,0015	MgO = 0,03%
KCl . . .	" " 0,0063	KCl = 0,12%
NaCl . . .	fällt " 0,0306	NaCl = 0,60%



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Redigiert von

C. Neuberg-Berlin.

*Sonderabdruck aus 63. Band, 2. und 3. Heft.*

John C. Hemmeter:

Zur Biochemie des Vagusproblems. II.



Berlin.

Verlag von Julius Springer.

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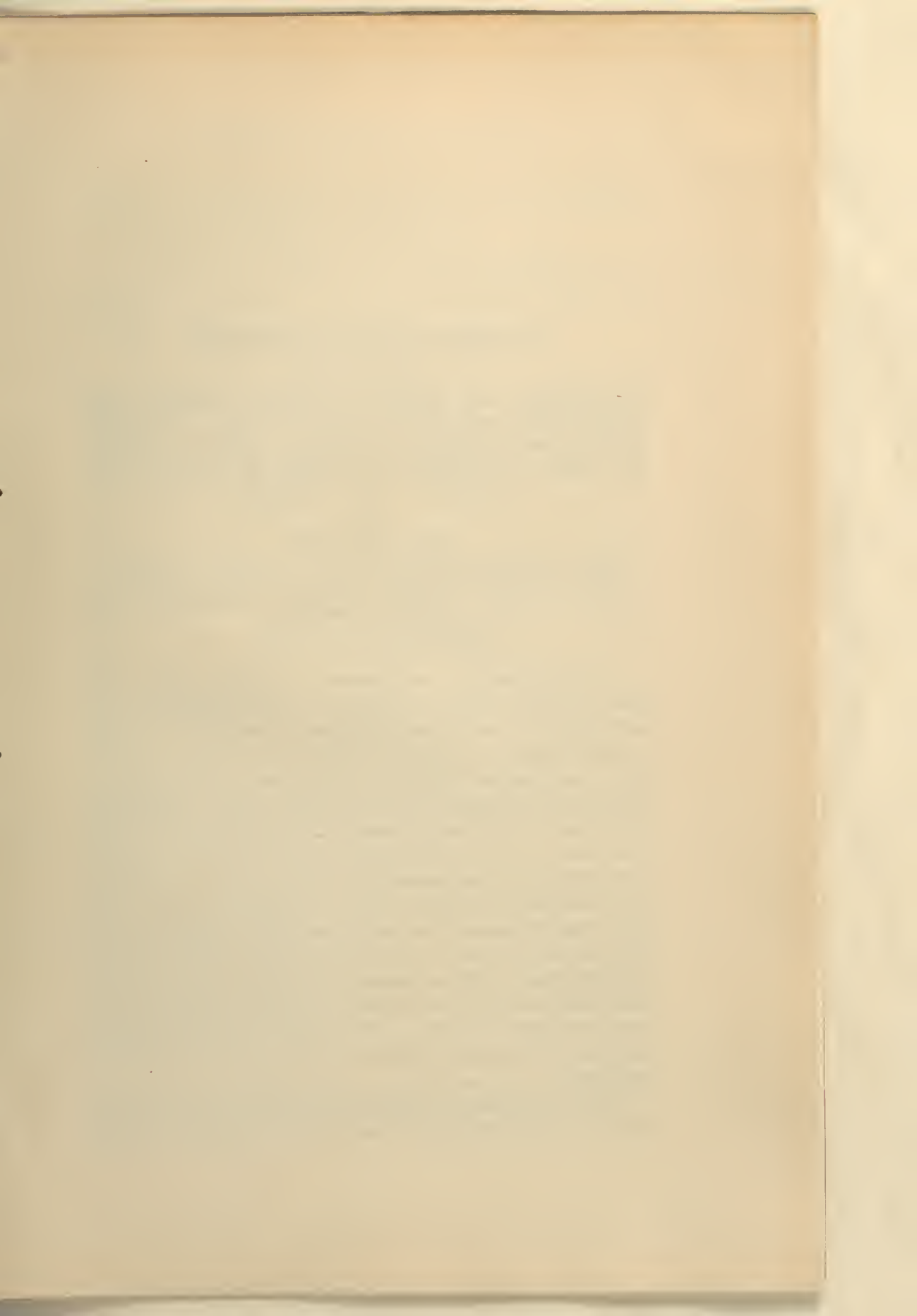
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## Zur Biochemie des Vagusproblems.

### II. Mitteilung.

Wechselseitige oder gekreuzte Zirkulation zwischen zwei Selachierherzen zur Entscheidung der Frage, ob Vagushemmung des einen Herzens Verlangsamung oder Aufhebung der Funktion des anderen durch Leitung des Blutes von „A“ nach „B“ verursachen kann.

Von

John C. Hemmeter.

(Aus dem biologischen Laboratorium des U. S. Bureau of Fisheries, Woods Hole, Mass., und dem physiologischen Laboratorium der Universität von Maryland.)

(Eingegangen am 9. März 1914.)

In der Zeitschr. f. biol. Technik u. Methodik 2, 372, 1911 habe ich die operative Technik mit allen Einzelheiten beschrieben, die diese gekreuzte Zirkulation zwischen den Herzen zweier Hundshaie ermöglicht. Zweck dieser Untersuchungen war, die chemische Natur der Vagushemmung zu ergründen. Wenn die Verzögerung oder der Stillstand des Herzschlages darauf beruht, daß eine Substanz aus dem Herzmuskel in Freiheit gesetzt wird und sich im Plasma auflöst, dann müßte das Blut des gehemmten Herzens das Vermögen besitzen, die Tätigkeit eines zweiten Herzens, in das es geschickt wird, zu verlangsamen oder gänzlich zu arretieren. Zur Lösung dieser Aufgabe müssen wir über eine operative Methode verfügen, die es gestattet, das im Herzen während der Vagushemmung befindliche Blut heraus in ein zweites Herz eines anderen Tieres derselben Spezies zu leiten. Ich möchte hier nur in kurzen Umrissen die in der erwähnten Arbeit beschriebene Technik skizzieren.

Zwei ganz gesunde Haifische (*Carcharias littoralis*) wurden direkt aus den Fangnetzen um 9<sup>1</sup>/<sub>2</sub> Uhr morgens in einem

großen mit Seewasser gefüllten Aquarium untergebracht. Nach lebhaftem Umherschwimmen wiedereetzten sie sich mit großer Kraft und Hartnäckigkeit der Äthernarkose.

Freilegung der Herzen. Einbindung von Kanülen in das proximale und distale Ende der thorakalen Aorta des Hais Nr. 1. Einsetzen von Kanülen in die seitliche Bauchvene und in das proximale Ende der Aorta thoracica von Hai Nr. 2.

Als Antikoagulans wurde Hirudin benutzt. Es ist eine kostspielige Substanz, denn 1 g kostet 19 \$ (ca. 75 M.). 1 ceg genügt, um das Blut von drei Hundshaien, von 2 kg Einzelgewicht, ungerinnbar zu machen. Bei einem Hundshai beträgt das Blut  $\frac{1}{10}$  des Körpergewichts, also enthält ein Cynais von 2000 g Schwere 200 g Blut. Damit dieses nicht gerinnt, sind 0,04 g Hirudin erforderlich. Man macht sich eine Lösung von 0,1 g Hirudin in 25 ccm Kochsalzlösung, und von dieser genügen 10 ccm, um das Blut eines 2 kg (4,4092 englische Pfund) wiegenden Hundshaies vor der Gerinnung zu schützen. In einem Versuch lösten wir einfach 1 cg Hirudin in 100 ccm Ringerscher Lösung auf und spülten damit vor Beginn des Versuches das ganze System der Gummi- und Glasröhren wie auch die Kanülen aus. In diesem Falle kam 2 Stunden lang keine Koagulation zustande. Vielleicht ist es überhaupt nicht durchaus notwendig, das Blut des Fisches inkoagulabel zu machen, da diese Vorsichtsmaßregel zu viel Hirudin benötigt. Wenn es in den Röhren und Kanülen nicht zur Gerinnung kommt — und das ist die Hauptsache —, dann ist wenig zu befürchten. Hirudin beeinflusst die Vagushemmung in keiner Weise, da sie nach Injektion dieses Antikoagulans unverändert bleibt.

Das proximale Ende der abdominalen oder vielmehr thorakalen Aorta des Hais Nr. 1 wurde mit einer Kanüle in der rechtsseitlichen Bauchvene des Hais Nr. 2 verbunden. Diese Kanüle wurde so weit wie möglich nach oben gestoßen und konnte im Cuvierschen Sinus gefühlt werden. Jede Zirkulation wurde durch Abklemmen mit Peans verhindert, bis alles zur gekreuzten Durchströmung bereit war. So konnte also das Blut von Hai Nr. 1 in das Herz von Hai Nr. 2 gelangen. Aber weiter mußte die Versuchsanordnung eine solche sein, daß ersteres daraus wieder zurück zum Spender, also Hai Nr. 1, zurückfließen und sich in den Kiemen von Nr. 1 oxydieren konnte.

Zu diesem Behufe wurde eine Verbindung hergestellt zwischen dem proximalen Ende der thorakalen Aorta von Nr. 2 und dem distalen derjenigen von Nr. 1. Nun strömt das Blut von Nr. 2 aus dem Ventrikel durch die Aorta und die gekreuzte Glasröhre in das distale Ende der thorakalen Aorta von Nr. 1, weiter in die Kiemen und zurück ins Herz von Nr. 1 durch seine eigene dorsale Aorta hindurch. Der Kreislauf nach den Bauchorganen und dem Schwanz ist durch Ligaturen unterbrochen.

Die gekreuzte Zirkulation gestaltet sich nun wie folgt: Aus dem Herzen von Nr. 1 durch die Kanüle am eigenen proximalen Ende der Bauchaorta und gekreuzte Glasröhre nach der lateralen Bauchvene und Cuvierschem Sinus, Venensinus und Herz von Nr. 2. Heraus aus der abdominalen Aorta von Nr. 2 durch die Kanüle und eine zweite gekreuzte Glasröhre zurück zu Nr. 1, durch die Kanüle am distalen Ende der ventralen oder besser thorakalen Aorta von Nr. 1 hindurch, von dort durch die Kiemen von Nr. 2, die unter Seewasser gehalten wurden, dann durch dorsale Aorta zurück in den allgemeinen Kreislauf (unter Ausschaltung des Schwanzes, nicht aber notwendigerweise der Baueingeweide) und schließlich nach dem Sinus venosus und Herzen von Nr. 1. In letzterem vermischt sich das Blut der beiden Fische bis zu einem gewissen Grade. Mit der Stoppuhr wurde immer genau bestimmt, wie lange Zeit das Blut des Hais Nr. 1 zum Zurücklegen der Strecke von der Kanüle am proximalen Ende der Aorta von Nr. 1 nach dem Sinus venosus von Nr. 2 brauchte. Aus diesem Grunde waren alle Verbindungsstücke so weit wie möglich aus Glas und nur, wo es unbedingt nötig war, aus Gummi. Da die Kanüle in dem proximalen Ende der Aorta von Nr. 1 mit Hundshaiserum, ebenso die Schlauchverbindungen zwischen Herz 1 und 2 mit Hai- oder Hundshaiserum gefüllt waren, so konnte der Strom in der Richtung nach vorwärts leicht verfolgt werden. Die Zeit, in der das Blut aus dem Herzen von Nr. 1 nach Nr. 2 gelangte, schwankte nach 1. der Kraft des Herzens, 2. der Weite des Glasrohrsystems, 3. der Länge der benutzten Rohrleitung. In unseren ersten Versuchen verwandten wir zu weite und zu viele Röhren, auch fehlte es uns an Übung, die Kanülen so einzusetzen, daß keine Luft-



blasen entstanden und die Verbindungen völlig luftdicht zu gestalten. Infolge dieser Mängel in der Technik mißlangen uns eine Anzahl von Versuchen. Aber wie lange Zeit auch verging, bis das Blut des Herzens von Nr. 1 in dasjenige von Nr. 2 kam, so mußte die Berechnung von dem Augenblicke an einsetzen, in dem die Vagusreizung von Nr. 1 aufhörte. Um aus den registrierten Zusammenziehungen des Herzens Nr. 2 beurteilen zu können, ob es durch eine aus Herz Nr. 1 stammende chemische Substanz gehemmt werden könne, ist es von vornherein klar, daß eine bestimmte Zeitdauer zwischen dem Moment, in dem Reizung des Vagus von Herz Nr. 1 dieses zum Stillstand bringt und zur darauffolgenden Wiederaufnahme des Schlages vergehen muß. Denn das Blut, das durch das verlangsamte oder ganz gehemmte Herz Nr. 1 fließt, kann das Herz Nr. 2 erst erreichen, wenn die Glas- und Gummiverbindungen und die seitliche Bauchvene von Nr. 2 passiert sind. Während vollständigen Stillstandes des Herzens Nr. 1 kann natürlich kein Blut von Nr. 1 in das Herz Nr. 2 gelangen.

Beide Herzen wurden auf gleicher Höhe gehalten. Jedes registrierte selbst seine ventrikularen Contractionen auf einem Kymographion, indem die Ventrikelspitze mit einem Schreibhebel durch einen Faden verbunden war. Der Vagus des Haies Nr. 1 war isoliert und mit einem Faden (der nicht zu dünn sein darf, um den Nerv nicht durchzuschneiden) gesichert. Reizung erfolgte durch einen Harvard-(Du Bois-)Induktionsapparat und einen Strom von sieben Volt. Die Entfernung der primären von der sekundären Spule betrug 10 cm. Vagusreizung verursachte prompt Hemmung dieses Herzens. Einmal wurde das Herz von Nr. 1 zu einem 1 Minute 6 Sekunden lang dauernden Stillstand gebracht, der nur durch zwei Contractionen unterbrochen wurde. Die Registrierung des Herzens Nr. 2 zeigte während der ganzen Zeit keine Veränderung in bezug auf Rhythmus, Tempo oder Kraft. Das Blut floß ungehindert aus den Kanülen in beiden Aorten, als sie nach 1 Stunde 16 Minuten abgebunden wurden. Man erhielt in fünf Versuchsreihen dieser Art sehr befriedigende Kurven.

Während eines absoluten Herzblocks kann kein Blut aus dem vagusgereizten Herzen in das ungereizte Herz gelangen, da, wenn das Herz sich nicht kontrahiert, das Blut nicht vor-



wärts bewegt wird. Sobald aber die Vagusreizung aufhört und der Ventrikel sich wieder zusammenzieht, setzt der Kreislauf von neuem ein. Man muß also vor allen Dingen darauf achten, daß die Zeitkurve auf dem Kymographion möglichst genau und vollständig wird, muß ferner den Gang der Ereignisse mit einer zuverlässigen Stoppuhr verfolgen und von dem Augenblicke an zählen, wo der Ventrikel wieder zu schlagen anfängt.

Beim Selachierherzen zweigen die Coronararterien nicht unmittelbar vom Ventrikel ab, sonst könnte der Herzmuskel nicht mit oxydiertem Blut versorgt werden. Das Blut in den Ventrikeln ist zum großen Teil gemischt, in Wirklichkeit mehr venösen als arteriellen Ursprungs, und wird erst in den Kiemen zur Oxydation getrieben. Dann treten die Coronararterien wieder aus den Kiemen aus und sind an der Oberfläche auf der Bauchseite der ventralen Aorta sichtbar<sup>1)</sup>.

Die Coronararterien des Herzens von Elasmobranchiern sind also zum größten Teile Gefäße, die außerhalb des eigentlichen Herzgewebes liegen und durch Zweige der mittleren Hypobranchialarterie gebildet werden. Bei einer Ventrikelcontraction geht das ausgepreßte Blut erst durch den Arterienbulbus, dann durch die ventrale Aorta, weiter durch das vielverzweigte Netz der Kiemengefäße, dann zurück durch die Vereinigung der sogenannten Commissurararterien. Diese Vereinigung hat den Namen „mittlere Hypobranchialader“ bekommen. Aus ihr gehen die afferenten Coronararterien hervor. (Siehe Parker, l. c. S. 164.)

Ich führe dies näher aus, um verständlich zu machen, daß es 3 bis 6 Sekunden dauern kann, bis das identische, aus den Ventrikeln gestoßene Blut als Coronarblut in den Muskel des Ventrikels zurückkommt, um ihn mit Sauerstoff und den wesentlichen Faktoren der Muskelcontraction zu versorgen. Es ist eine bekannte und aus den hier mitgeteilten Kurven wohl ersichtliche Tatsache, daß das Herz innerhalb eines Bruchteils einer Sekunde nach gelungener Vagusreizung völlig gehemmt werden kann. In Wirklichkeit dauert es wohl noch kürzer, da es nicht möglich ist, mit absoluter Genauigkeit die Zeit der latenten Periode der Vagusreizung zu registrieren.

<sup>1)</sup> Die Blutgefäße des Herzens von *Carcharias*, *Raja* und *Amia* von G. H. Parker, Proc. of the Boston Soc. of Natural History 29, Nr. 8, 1899.

Da mindestens einige Sekunden vergehen, bis das Blut in den Bereich der Kiemenzirkulation und zurück in das Herz gelangt, so ist nicht einzusehen, wie die Herzhemmung durch eine chemische Substanz bedingt werden sollte, die im Herzen entsteht, aus dem Myocardium freigemacht wird und durch die Gefäße des Thebesius entweicht, welche mit den Coronarvenen freier kommunizieren als die Kranzschlagadern. Wenn die Hemmung durch das Freiwerden eines in dem Herzmuskel gebundenen chemischen Stoffes zustande kommt, so muß sie aus dem Myocardium durch die Venen austreten, dann aus dem Ventrikel mit der nächsten Systole ausgestoßen werden, weiter in die Kiemen gelangen und durch die Coronararterie zurückkehren. Dieser ganze Weg nimmt aber längere Zeit in Anspruch, als zur vollständigen Hemmung notwendig ist. Oder anders ausgedrückt, der Herzmuskel dieser Selachier wird nicht mit Blut versorgt, das aus dem Ventrikel mit jeder Systole ausgeworfen wird, sondern es wird durch die systolische Bewegung nach den Kiemen getrieben, muß durch die Kranzschlagadern zurückfließen, und dann erst speist es den Herzmuskel. Wenn der Kiemenkreislauf länger dauert, als es Zeit (Sekunden) bedarf, durch Vagusreizung eine Herzhinhibition zu verursachen, dann kann eo ipso dieser Herzstillstand keiner chemischen Substanz zugeschrieben werden, die unter dem Einfluß der Vagusreizung im Myocardium entsteht. Folglich muß die Zeit, in der die Vagushemmung des Herzens nach Reizung dieses Nerven erfolgt, im Vergleich mit der, die vergeht, bis das ventrikuläre Blut die branchiale Zirkulation zurückgelegt hat, als ein sehr ins Gewicht fallender Faktor bei der Kritik einer Theorie betrachtet werden, die die Vagushemmung durch Abspaltung von KCl aus dem Myocardium dieser Tiere zu erklären versucht. Die gesteigerte Ausscheidung von diesem Salz während der Vagushemmung scheint mehr eine Folge dieser Erscheinung als ihre Ursache zu sein, denn nach einem so absoluten Schlaffwerden des Herzmuskels in solch einer ausgedehnten Diastole ist es denkbar, daß mehr lösliche Elektrolyten durch den darauf einsetzenden Blutstrom mitgerissen werden, sobald das Herz wieder zu schlagen anfängt. Zahlreiche Physiologen haben Lucianis Auffassung des Vagus als diastolischer Nerv des Herzens akzeptiert, die Anschauung nämlich, daß der Vagus nicht nur alle Muskel-

fasern zum Stillstand bringt, sondern sie auch in den Zustand völliger Erschlaffung versetzt.

### Erklärung der Kymographionkurven.

Die beifolgenden kymographischen Kurven bestehen, wie leicht zu übersehen, aus 4 Einzelregistrierungen. Die beiden obersten sind die aus den Ventrikeln direkt erhaltenen Ventrikularkurven von zwei als Nr. 1 und Nr. 2 bezeichneten Hunds-haien. Darunter befindet sich die Zeitkurve in Sekunden und unterhalb dieser als letzte die Aufzeichnung des Reizhebels. In einigen Versuchen registrierte dieser auf der dritten anstatt vierten Zeile. Zur Erklärung der Unregelmäßigkeiten der Ventrikularkurven muß ich den Umstand hervorheben, daß bei Gebrauch der Suspensionsmethode die geringste Unruhe des Fisches genügt, damit die Registrierspitze die berußte Fläche des rotierenden Papiers verläßt. Da Fische nicht so gut wie Säugetiere oder Amphibien angebunden werden können (die Gründe dafür sind in der Arbeit „Zur Technik von Vagus-experimenten am Herzen von *Scyllium*, *Mustelus canis*, *Cynais canis*, *Carcharias littoralis*, *Squalus acanthis*“<sup>1)</sup> auseinander-gesetzt), so ist eine tiefe Narkose unbedingt zum Gelingen des Versuchs geboten. Eine solche ist aber, während die Tiere mit dem Kymographion verbunden sind, nicht möglich. Infolgedessen kommt es zuweilen vor, daß sie sich im kritischen Moment im Halter drehen. Dadurch schon wird für den Beobachter die Aufzeichnung gerade in dem ihm wichtigsten Augenblick nicht nur wertlos, sondern das ganze Papier wird zuweilen auch mit Seewasser bespritzt. Daher sind die Kurven nicht von so tadelloser Akkurateesse, wie es bei einem Säugetier oder Frosch der Fall zu sein pflegt. Doch besitzen wir Aufzeichnungen von 5 Versuchen, die ganz glatt, ohne solche Störung, verliefen. Aus ihnen geht hervor, daß das Herz Nr. 2, das mit seinem Blut Nr. 1 speiste, vollständig gehemmt war, daß dagegen das Herz von Nr. 1, das mit Blut dieses inhibierten Herzens beschickt wurde, niemals irgendwelche Verlangsamung in der rhythmischen Funktion aufwies. In der August 1911 datierten Registrierung dauerte eine Hemmung 27 Sekunden, wonach eine Contraction erfolgte, eine weitere

<sup>1)</sup> Zeitschr. f. biol. Technik u. Methodik 2, Nr. 5, S. 221, 1911.

Hemmung 7 Sekunden mit nachfolgender Zuckung, eine dritte 9 Sekunden — danach Unterbrechung durch einen Schlag, wieder eine 6 Sekunden mit einer vierten Unterbrechung. Die fünfte Hemmungsperiode umfaßte 5 Sekunden, worauf das Herz wieder normal zu funktionieren begann, da die Reizung des Vagus abgebrochen wurde. Während dieser ganzen Zeitdauer von 54 Sekunden trat in der Kurve von Nr. 1 nicht die geringste Veränderung im Rhythmus auf, auch nicht in den auf die Hemmungsperiode beobachteten folgenden 15 Minuten. Bevor man irgendwelche Schlüsse aus den Kurven ziehen will, muß man sich die Frage vorlegen, wie lange Zeit das Blut braucht, um aus dem Herzen des liefernden in dasjenige des empfangenden Fisches zu gelangen. Bei dieser Untersuchung ist das die Gerinnung hemmende Hirudin unerlässlich, denn bei der Verwendung so zahlreicher Verbindungsschläuche bilden sich zweifellos Gerinnsel, noch ehe man Beobachtungen anstellen kann. Hier könnte man den Einwand erheben, daß Hirudin an und für sich schon vielleicht die Herzhemmung beeinflußt. Daß diese Befürchtung in Wirklichkeit grundlos ist, beweist die Tatsache, daß ein Herz auf Vagus-hemmung prompt reagierte, das andere dagegen versagte. Folglich kann Hirudin den Herzstillstand nicht verhindern — mithin wird der Einwand hinfällig, daß dadurch die Eindeutigkeit der Versuchsergebnisse in Zweifel gezogen werden kann. Möglicherweise beruht aber die Hemmung, könnte man fragen, überhaupt nicht auf der Abspaltung von Kalium in dem blutversorgenden Herzen, sondern auf dem Verlust an Kalium, ehe es das zu speisende Herz erreicht? Ein Blick auf die methodische Anordnung lehrt aber, daß ein Verlust ausgeschlossen ist, weil der Blutstrom infolge der Unterbindung aller Ausflußwege außer nach dem Vencnsinus auf seinem Wege zu dem zweiten oder empfangenden Herzen gar kein Organ passierte.

Daß die Diastole des Herzens eine Hemmungserscheinung ist, bespricht Howell in seiner Arbeit über „Studium des Einflusses der Na-, K- und Ca-Salze des Blutes auf die automatischen Contractionen des Herzmuskels“<sup>1)</sup>. Diesbezüglich verweisen wir auch auf die Forschungen von Fanò, Meltzer,

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<sup>1)</sup> Amer. Journ. of Physiol. 6, 205.



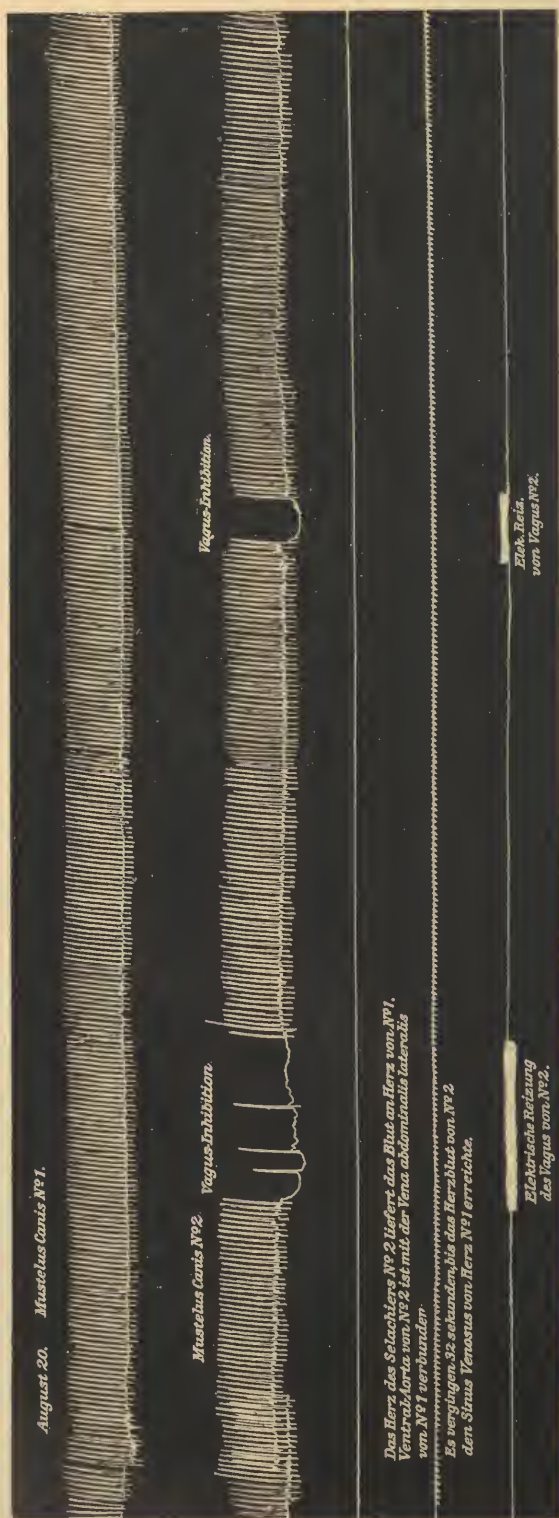
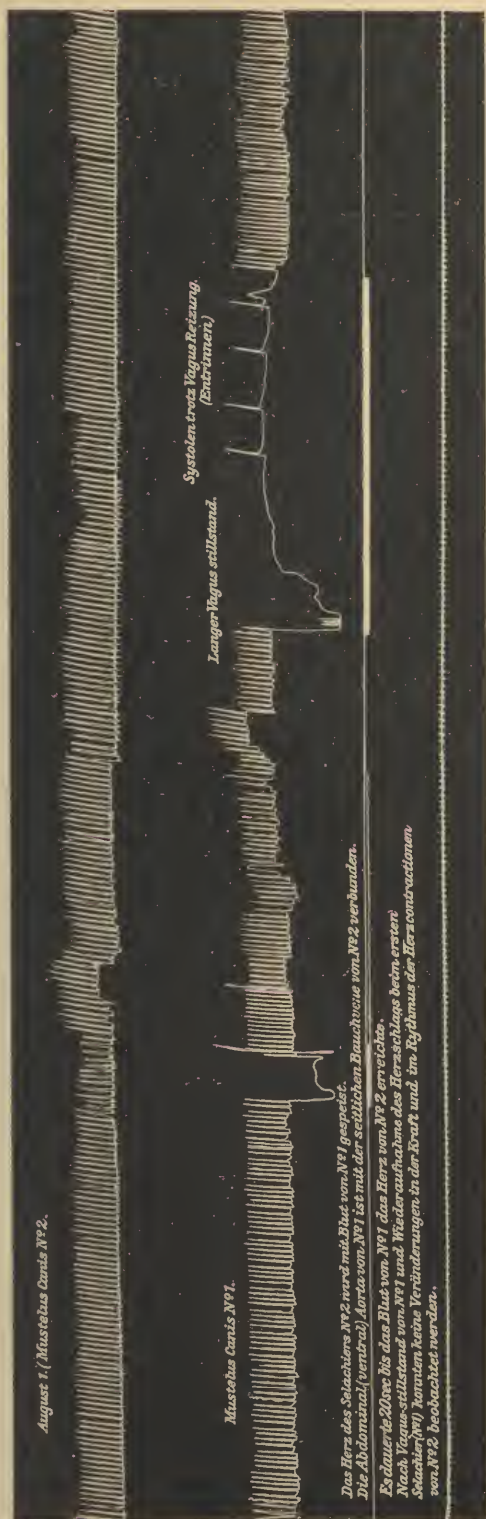


Fig. 1.

Ranke, Bottazzi und Aubert. Als erster hat Luciani diese Behauptung aufgestellt. In dem 1. Band seiner vortrefflichen „Fisiologia dell' Uomo“, S. 175, lesen wir seine eigene und Stefanis Bestätigung seiner Versuche, die dar- tun, daß der Vagus der diastolische Nerv des Herzens in dem Sinne ist, daß er durch Ver- änderung der physio- logischen Bedingungen des Herzmuskels das Herzvolumen vergrößert. Lucianis erste Versuche in dieser Rich- tung wurden 1871 aus- geführt.

Solch eine allgemeine Auflockerung des Herz- gewebes, wie sie die Autoren beschreiben und die auch histo- logisch bei Herzen, die im Lähmungszustande unterbunden und ge- froren werden, nach- gewiesen werden kann, würde natürlich eine leichtere Ausschwe- mung der löslichen an- organischen Salze durch den Blutstrom erklären. Dies würde sich der Theorie von Howell

Fig. 2.



gut einfügen, die jedoch weder durch unsere Analysen der Asche von Blut aus gehemmten Herzen, noch durch die Ergebnisse der gekreuzten oder wechselseitigen Zirkulation bestätigt werden konnte.

Es sind so viele Möglichkeiten für den Verlust oder die Wiederverbindung von löslichen Kaliumsalzen vorhanden, daß wir uns beschränken müssen, unsere Meinung vorläufig so zu formulieren: aus einem gehemmten Herzen wird in das durchfließende Blut nichts ausgeschieden, wodurch die Tätigkeit eines zweiten Herzens derselben Spezies (bei Versuchen am Hundshai oder Hai) verlangsamt oder zum Stillstand gebracht werden kann.

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Meinen Assistenten Herren Dr. Albert H. Carroll, Thomas Patterson und D. E. Worrall, sowie den Herren Professoren R. J. Meyer und A. Rosenheim in Berlin meinen Dank. Den ersteren für ihre operative und physiologische Unterstützung, den Berliner Kollegen für ihre genauen chemischen Kontrollanalysen.

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